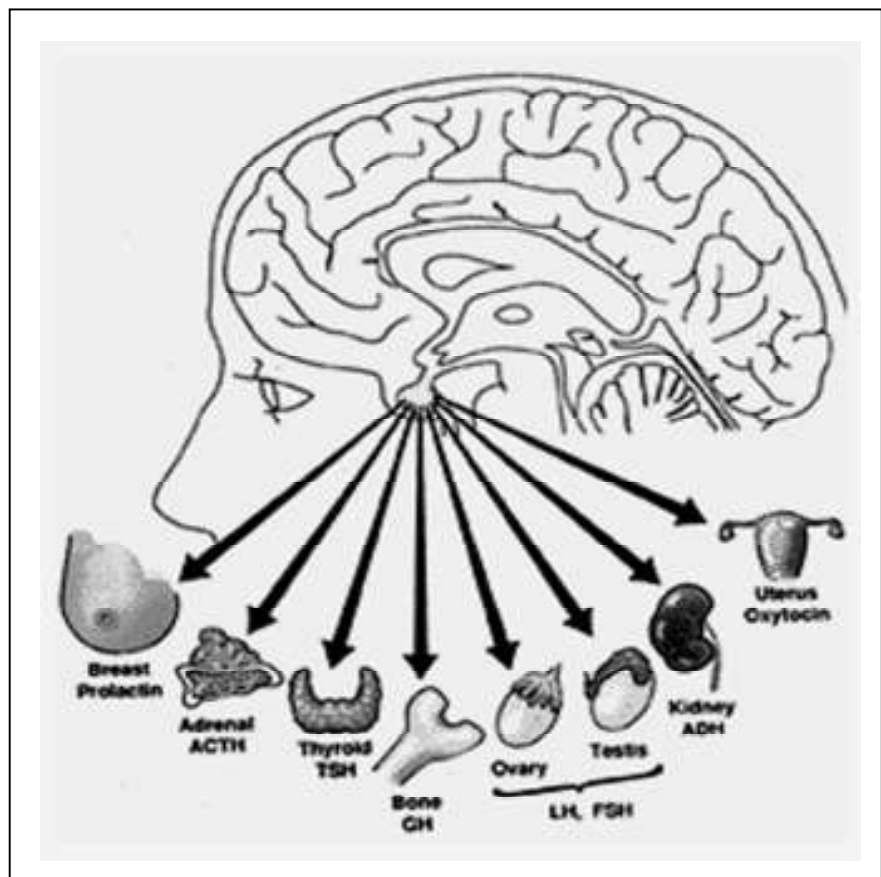


# Part *I* *Endocrinology*

*M. Estari*

- 1. Major endocrine glands*
- 2. Hormones and their functions*
- 3. Mechanism of hormone action*

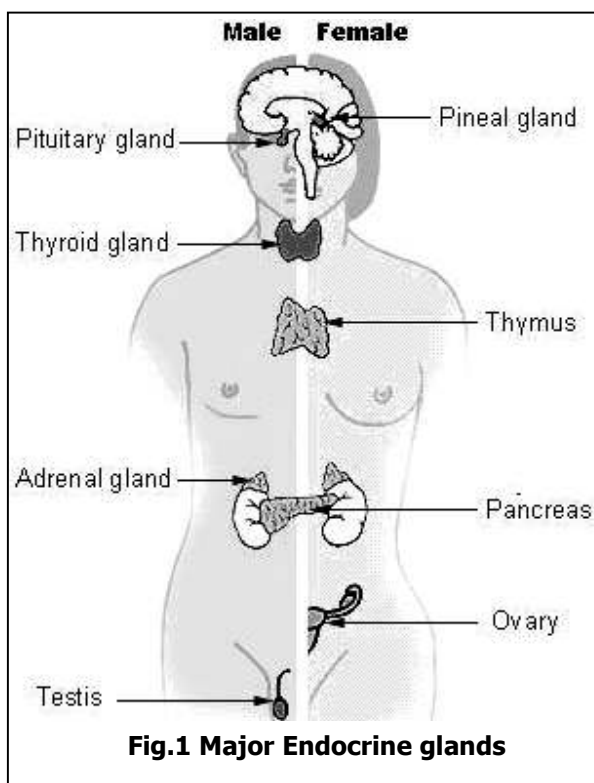


## 1. MAJOR ENDOCRINE GLANDS

- 1.1. INTRODUCTION
- 1.2. PITUITARY GLAND
- 1.3. THYROID & PARATHYROID GLANDS
- 1.4. ADRENAL GLAND
- 1.5. PANCREAS-ISLETS OF LONGERHANS
- 1.6. GONADS (TESTIS & OVARIES)
- 1.7. OTHER ENDOCRINE GLANDS

### 1.1. INTRODUCTION

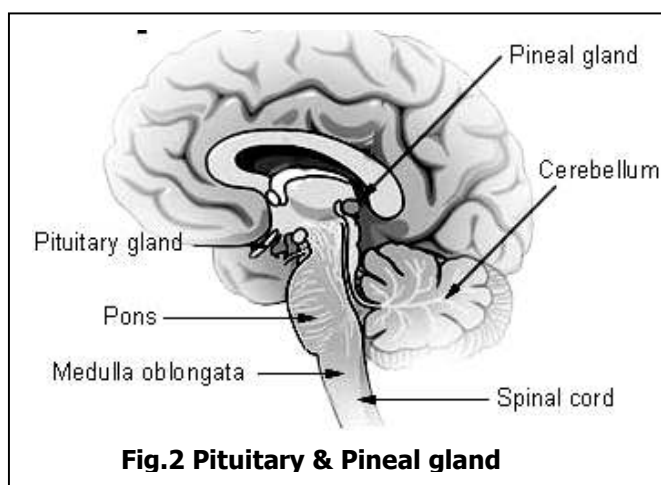
- **Endocrine glands** are glands that secrete their product directly into the blood rather than through a duct. This group contains the glands of the Endocrine system.
- The endocrine system is made up of the endocrine glands that secrete hormones. Although there are eight major endocrine glands scattered throughout the body, they are still considered to be one system because they have similar functions, similar mechanisms of influence, and many important interrelationships.
- Some glands also have non-endocrine regions that have functions other than hormone secretion. For example, the pancreas has a major exocrine portion that secretes digestive enzymes and an endocrine portion that secretes hormones. The ovaries and testes secrete hormones and also produce the ova and sperm.



- Some organs, such as the stomach, intestines, and heart, produce hormones, but their primary function is not hormone secretion.
- The following are the major endocrine glands: **(Fig.1)**
  - Pituitary & Pineal gland
  - Thyroid & Parathyroid Glands
  - Adrenal (Suprarenal) Gland
  - Pancreas --- Islets of Langerhans
  - Gonads (Testes and Ovaries)

## 1.2 PITUITARY & PINEAL GLANDS

- The pituitary gland or hypophysis is a small gland about 1 centimeter in diameter or the size of a pea. It is nearly surrounded by bone as it rests in the sella turcica, a depression in the sphenoid bone. The gland is connected to the hypothalamus of the brain by a slender stalk called the infundibulum.
- There are two distinct regions in the gland: the **anterior lobe** (adenohypophysis) and the **posterior lobe** (neurohypophysis). The activity of the adenohypophysis is controlled by releasing hormones from the hypothalamus. The neurohypophysis is controlled by nerve stimulation.



### 1.2.1. Hormones of the Anterior Lobe (Adenohypophysis)

- Growth hormone is a protein that stimulates the growth of bones, muscles, and other organs by promoting protein synthesis. This hormone drastically affects the appearance of an individual because it influences height. If there is too little growth hormone in a child, that person may become a pituitary dwarf of normal proportions but small

stature. An excess of the hormone in a child results in an exaggerated bone growth, and the individual becomes exceptionally tall or a giant.

- Thyroid-stimulating hormone, or thyrotropin, causes the glandular cells of the thyroid to secrete thyroid hormone. When there is a hypersecretion of thyroid-stimulating hormone, the thyroid gland enlarges and secretes too much thyroid hormone.
- Adrenocorticotrophic hormone reacts with receptor sites in the cortex of the adrenal gland to stimulate the secretion of cortical hormones, particularly cortisol.
- Gonadotropic hormones react with receptor sites in the gonads, or ovaries and testes, to regulate the development, growth, and function of these organs.
- Prolactin hormone promotes the development of glandular tissue in the female breast during pregnancy and stimulates milk production after the birth of the infant.

### 1.2.2 Hormones of the Posterior Lobe (Neurohypophysis):

- **Antidiuretic hormone** promotes the reabsorption of water by the kidney tubules, with the result that less water is lost as urine. This mechanism conserves water for the body. Insufficient amounts of antidiuretic hormone cause excessive water loss in the urine.

- **Oxytocin** causes contraction of the smooth muscle in the wall of the uterus. It also stimulates the ejection of milk from the lactating breast.

### 1.2.3 Pineal Gland:

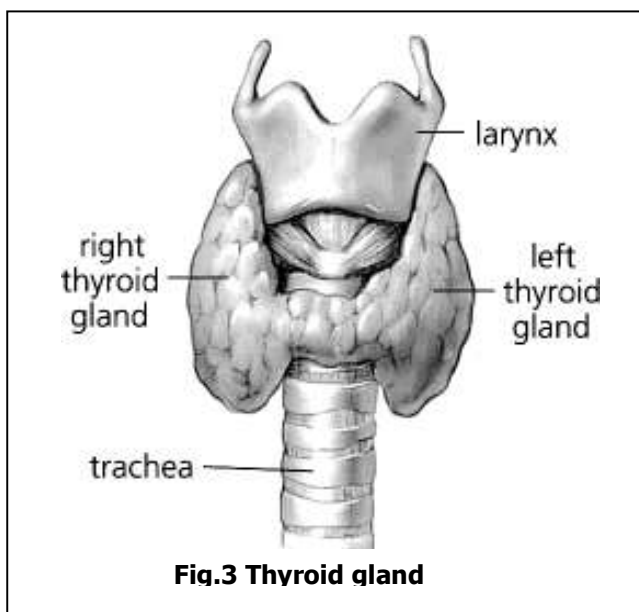
- The **pineal gland**, also called pineal body or epiphysis cerebri, is a small cone-shaped structure that extends posteriorly from the third ventricle of the brain. The pineal gland consists of portions of neurons, neuroglial cells, and specialized secretory cells called pinealocytes. The pinealocytes synthesize the hormone melatonin and secrete it directly into the cerebrospinal fluid, which takes it into the blood. Melatonin affects reproductive development and daily physiologic cycles.

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## 1.3 THYROID GLAND

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- The **thyroid gland** is a very vascular organ that is located in the neck. It consists of two lobes, one on each side of the trachea, just below the larynx or voice box. The two lobes are connected by a narrow band of tissue called the isthmus. Internally, the gland consists of follicles, which produce thyroxine and triiodothyronine hormones. These hormones contain iodine.



- About 95 percent of the active thyroid hormone is thyroxine, and most of the remaining 5 percent is triiodothyronine. Both of these require iodine for their synthesis. Thyroid hormone secretion is regulated by a negative feedback mechanism that involves the amount of circulating hormone, hypothalamus, and adenohypophysis.
- If there is an iodine deficiency, the thyroid cannot make sufficient hormone. This stimulates the anterior pituitary to secrete thyroid-stimulating hormone, which causes the thyroid gland to increase in size in a vain attempt to produce more hormones.
- But it cannot produce more hormones because it does not have the necessary raw material, iodine. This type of thyroid enlargement is called simple goiter or iodine deficiency goiter
- **Calcitonin** is secreted by the parafollicular cells of the thyroid gland. This hormone opposes the action of the parathyroid glands by reducing the calcium level in the blood. If blood calcium becomes too high, calcitonin is secreted until calcium ion levels decrease to normal.

### 1.3.1 Parathyroid Gland:

- Four small masses of epithelial tissue are embedded in the connective tissue capsule on the posterior surface of the thyroid glands. These are parathyroid glands, and they secrete or parathormone. Parathyroid hormone is the most important regulator of blood **parathyroid hormone** calcium levels. The hormone is secreted in response to low blood calcium levels, and its effect is to increase those levels.
- **Hypoparathyroidism**, or insufficient secretion of parathyroid hormone, leads to increased nerve excitability. The low blood calcium levels trigger spontaneous and continuous nerve impulses, which then stimulate muscle contraction.

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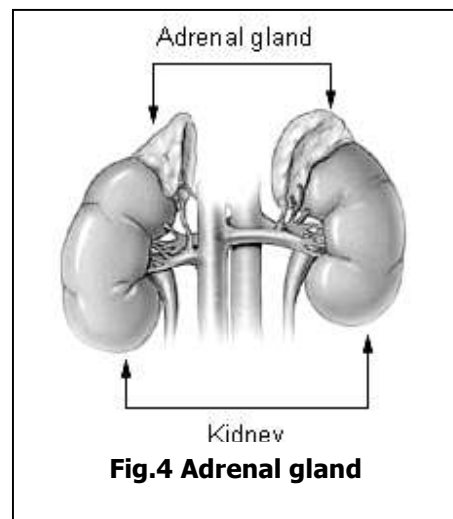
## 1.4 THE ADRENAL

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- The adrenal, or suprarenal, gland is paired with one gland located near the upper portion of each kidney. Each gland is divided into an outer cortex and an inner medulla.
- The cortex and medulla of the adrenal gland, like the anterior and posterior lobes of the pituitary, develop from different embryonic tissues and secrete different hormones. The adrenal cortex is essential to life, but the medulla may be removed with no life-threatening effects.
- The hypothalamus of the brain influences both portions of the adrenal gland but by different mechanisms. The adrenal cortex is regulated by negative feedback involving the hypothalamus and adrenocorticotrophic hormone; the medulla is regulated by nerve impulses from the hypothalamus.

### 1.4.1. Hormones of the Adrenal Cortex:

- The adrenal cortex consists of three different regions, with each region producing a different group or type of hormones. Chemically, all the cortical hormones are steroid.
- **Mineralocorticoids** are secreted by the outermost region of the adrenal cortex. The principal mineralocorticoid is aldosterone, which acts to conserve sodium ions and water in the body.
- **Glucocorticoids** are secreted by the middle region of the adrenal cortex. The principal glucocorticoid is cortisol, which increases blood glucose levels.
- The third group of steroids secreted by the adrenal cortex is the **gonadocorticoids**, or sex hormones. These are secreted by the innermost region. Male hormones, androgens, and female hormones, estrogens are secreted in minimal amounts in both sexes by the adrenal cortex, but their effect is usually masked by the hormones from the testes and ovaries. In females, the masculinization effect of androgen secretion may become evident after menopause, when estrogen levels from the ovaries decrease



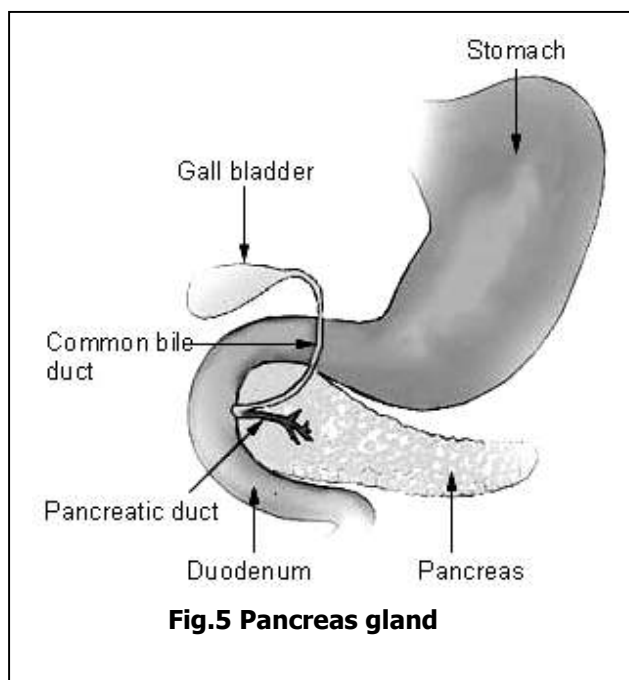
### 1.4.2. Hormones of the Adrenal Medulla:

- The adrenal medulla develops from neural tissue and secretes two hormones, **epinephrine** and **norepinephrine**. These two hormones are secreted in response to stimulation by sympathetic nerve, particularly during stressful situations. A lack of hormones from the adrenal medulla produces no significant effects. Hypersecretion, usually from a tumor, causes prolonged or continual sympathetic responses.

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## 1.5 THE PANCREAS

- The pancreas is a long, soft organ that lies transversely along the posterior abdominal wall, posterior to the stomach, and extends from the region of the duodenum to the spleen. This gland has an exocrine portion that secretes digestive enzymes that are carried through a duct to the duodenum. The endocrine portion consists of the pancreatic islets, which secrete glucagons and insulin.
- Alpha cells in the pancreatic islets secrete the hormone glucagons in response to a low concentration of glucose in the blood. Beta cells in the pancreatic islets secrete the hormone insulin in response to a high concentration of glucose in the blood.



**Fig.5 Pancreas gland**

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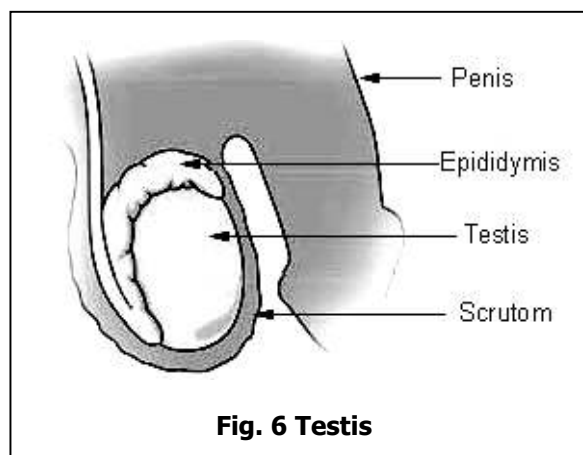
## 1.6 THE GONADS

- The gonads, the primary reproductive organs, are the testes in the male and the ovaries in the female. These organs are responsible for producing the sperm and ova, but they also secrete hormones and are considered to be endocrine glands.

### 1.6.1 Testes:

- Male sex hormones, as a group, are called androgens. The principal androgen is testosterone, which is secreted by the testes. A small amount is also produced by the adrenal cortex.
- Production of testosterone begins during fetal development, continues for a short time after birth, nearly ceases during childhood, and then resumes at puberty. This steroid hormone is responsible for:

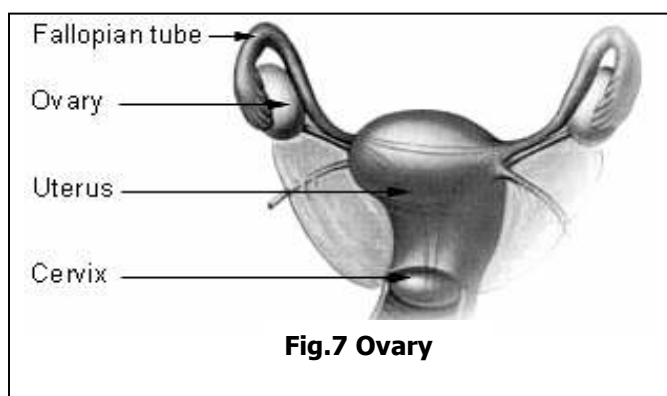
- The growth and development of the male reproductive structures
- Increased skeletal and muscular growth
- Enlargement of the larynx accompanied by voice changes
- Growth and distribution of body hair
- Increased male sexual drive
- Testosterone secretion is regulated by a negative feedback system that involves releasing hormones from the hypothalamus and gonadotropins from the anterior pituitary.

**Fig. 6 Testis**

### 1.6.2 Ovaries:

- Two groups of female sex hormones are produced in the ovaries, the estrogens and progesterone. These steroid hormones contribute to the development and function of the female reproductive organs and sex characteristics. At the onset of puberty, estrogens promotes:

- The development of the breasts,
- Distribution of fat evidenced in the hips, legs, and breast, and
- Maturation of reproductive organs such as the uterus and vagina

**Fig.7 Ovary**

- Progesterone causes the uterine lining to thicken in preparation for pregnancy. Together, progesterone and estrogens are responsible for the changes that occur in the uterus during the female menstrual cycle.

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## 1.7 OTHER GLANDS

- In addition to the major endocrine glands, other organs have some hormonal activity as part of their function. These include the thymus, stomach, small intestines, heart, and placenta.
- Thymosin, produced by the thymus gland, plays an important role in the development of the body's immune system.
- The lining of the stomach, the gastric mucosa, produces a hormone, called **gastrin**, in response to the presence of food in the stomach. This hormone stimulates the production of hydrochloric acid and the enzyme pepsin, which are used in the digestion of food.

- The mucosa of the small intestine secretes the hormones **secretin** and **cholecystokinin**. Secretin stimulates the pancreas to produce a bicarbonate-rich fluid that neutralizes the stomach acid. Cholecystokinin stimulates contraction of the gallbladder, which releases bile. It also stimulates the pancreas to secrete digestive enzyme.
- The heart also acts as an endocrine organ in addition to its major role of pumping blood. Special cells in the wall of the upper chambers of the heart, called atria, produce a hormone called atrial natriuretic hormone, or atriopeptin.
- The placenta develops in the pregnant female as a source of nourishment and gas exchange for the developing fetus. It also serves as a temporary endocrine gland. One of the hormones it secretes is human chorionic
- **Gonadotropin**, which signals the mother's ovaries to secrete hormones to maintain the uterine lining so that it does not degenerate and slough off in menstruation.

## 2. HORMONES AND THEIR FUNCTIONS

### 2.1 INTRODUCTION

#### 2.2 PITUITARY HORMONES

#### 2.3 THYROID HORMONES

#### 2.4 PARATHYROID HORMONES

#### 2.5 ADRENAL HORMONES

#### 2.6 PANCREATIC HORMONES

#### 2.7 GONADAL HORMONES

### 2.1 INTRODUCTION

- A **hormone** (from Greek - "to set in motion") is a chemical messenger from one cell (or group of cells) to another. All multicellular organisms produce hormones (including plants – *eg. phytohormone*).
- The function of hormones is to serve as a signal to the target cells; the action of hormones is determined by the pattern of secretion and the **signal transduction** of the receiving tissue. The best-known animal hormones are those produced by endocrine glands of vertebrate animals, but hormones are produced by nearly every organ *system and* tissue type in an animal body.
- Hormone molecules are secreted (released) directly into the **bloodstream**; some hormones, called **ectohormones**, are not secreted into the blood stream, they move by circulation or diffusion to their target cells, which may be nearby cells (paracrine action) in the same tissue or cells of a distant organ of the body.
- Most hormones initiate a cellular response by initially combining with either a specific **intracellular** or **cell membrane associated receptor** protein. A cell may have several different receptors that recognize the same hormone and activate different signal transduction pathways, or alternatively different hormones and their receptors may invoke the same biochemical pathway.
- For many hormones, including most protein hormones, the receptor is membrane associated and embedded in the plasma membrane at the surface of the cell. The **interaction of hormone** and receptor typically triggers a cascade of secondary effects within the cytoplasm of the cell, often involving phosphorylation or dephosphorylation of various other cytoplasmic proteins, changes in ion channel permeability, or increased concentrations of intracellular molecules that may act as secondary messengers (e.g. **cyclic AMP**).
- For hormones such as **steroid** or **thyroid hormones**, their receptors are located intracellularly within the cytoplasm of their target cell. In order to bind their receptors these hormones must cross the cell membrane. The combined hormone-receptor complex then moves across the nuclear membrane into the nucleus of the cell, where it binds to specific DNA sequences, effectively amplifying or suppressing the action of certain genes, and affecting protein synthesis. However, it has been shown that not

all steroid receptors are located intracellularly, some are plasma membrane associated.

- An important consideration, dictating the level at which cellular **signal transduction pathways** are activated in response to a hormonal signal is the effective concentration of hormone-receptor complexes that are formed. **Hormone-receptor complex** concentrations are effectively determined by three factors:
  - The number of receptor molecules available for complex formation,
  - The number of hormone molecules available for complex formation and
  - The binding affinity between hormone and receptor.
- The number of hormone molecules available for complex formation is the key factor in determining the level at which signal transduction pathways are activated. The other two factors usually remaining constant.
- The number of hormone molecules available is determined by the concentration of circulating hormone, which is in turn influenced by the level and rate at which it is secreted by biosynthetic cells.

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## 2.2 PITUITARY HORMONES

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- The **pituitary gland**, or **hypophysis**, is an endocrine gland about the size of a pea that sits in a small, bony cavity (pituitary fossa) covered by a dural fold (sellar diaphragm) at the base of the brain.
- The pituitary fossa, in which the pituitary gland sits, is situated in the sphenoid bone in the middle cranial fossa at the base of the brain.
- The pituitary gland secretes hormones regulating homeostasis, including trophic hormones that stimulate other endocrine glands. It is functionally connected to the hypothalamus by the median eminence.
- Located at the base of the brain, the pituitary is functionally linked to the hypothalamus. It is divided into two lobes: the **anterior** or front lobe (adenohypophysis) and the **posterior** or rear lobe (neurohypophysis).

### 2.2.1 Hormones of adenohypophysis

- The anterior lobe is derived from the oral ectoderm and is composed of glandular epithelium. The anterior pituitary is functionally linked to the hypothalamus via the hypophysial-portal vascular connection in the pituitary stalk. Through this vascular connection the hypothalamus integrates stimulatory and inhibitory central and peripheral signals to the five phenotypically distinct pituitary cell types.
- The anterior pituitary hormones, and the hypothalamic hormones that modulate their release are listed below, along with the associated cell types.

**Table:1 Functions of anterior pituitary hormones**

<b>Anterior pituitary hormone</b>	<b>Hypothalamic hormone</b>	<b>Staining type</b>	<b>Cell type</b>
growth hormone	release caused by GHRH (growth hormone releasing hormone)	acidophil	somatotrope
prolactin	release <b>INHIBITED</b> by DA (dopamine, "prolactin inhibiting factor"/PIF)	acidophil	lactotroph (or mammotroph)
follicle-stimulating hormone	release caused by GnRH (gonadotropin-releasing hormone)	basophil	gonadotrope
luteinizing hormone	release caused by GnRH (gonadotropin-releasing hormone)	basophil	gonadotrope
thyroid-stimulating hormone	release caused by TRH (thyrotropin-releasing hormone)	basophil	thyrotrope
adrenocorticotrophic hormone	release caused by CRH (corticotropin-releasing hormone)	chromatophil	corticotrope

**2.2.1-1. Growth hormone & its functions:**

- (**GH** or **somatotropin**) is a 191-amino acid, single chain polypeptide hormone which is synthesised, stored and secreted by the **somatotroph cells** within the lateral wings of the anterior pituitary gland, which stimulates growth and cell reproduction in humans and other animals.
- Effects of growth hormone on the tissues of the body can generally be described as **anabolic** (building up). Like most other protein hormones GH acts by interacting with a specific receptor on the surface of cells.
- Height growth in childhood is the best known effect of GH action, and appears to be stimulated by at least two mechanisms.
  - 1. GH directly stimulates division and multiplication of **chondrocytes** of cartilage. These are the primary cells in the growing ends (epiphyses) of children's long bones (arms, legs, digits).
  - 2. GH also stimulates production of **insulin-like growth factor 1** (IGF1, formerly known as somatomedin C), a hormone homologous to proinsulin. The liver is a major target organ of GH for this process, and is the principal site of IGF-1 production. IGF-1 has growth-stimulating effects on a wide variety of tissues. Additional IGF-1 is generated within target tissues, making it

apparently both an endocrine and an autocrine/paracrine hormone. IGF-1 will also have stimulatory effects on osteoblast and chondrocyte activity to promote bone growth.

**Other functions:**

- Although height growth is the best known effect of GH, it serves many other metabolic functions as well.
- It increases calcium retention, and strengthens and increases the mineralization of bone.
- It increases muscle mass through the creation of new muscle cells (which differs from hypertrophy)
- It promotes lipolysis, which results in the reduction of adipose tissue (body fat).
- It increases protein synthesis and stimulates the growth of all internal organs excluding the brain.
- It plays a role in fuel homeostasis.
- It reduces liver uptake of glucose, an effect that opposes that of insulin.
- It promotes liver gluconeogenesis.
- It also contributes to the maintenance and function of pancreatic islets.
- It stimulates the immune system.

**Clinical problems:****A) Growth hormone excess: (acromegaly and pituitary gigantism)**

- The most common disease of GH excess is a pituitary tumor comprised of somatotroph cells of the anterior pituitary. These somatotroph adenomas are benign and grow slowly, gradually producing more and more GH. For years, the principal clinical problems are those of GH excess. Eventually the adenoma may become large enough to cause headaches, impair vision by pressure on the optic nerves, or cause deficiency of other pituitary hormones by displacement.
- Prolonged GH excess thickens the bones of the jaw, fingers and toes. Resulting heaviness of the jaw and increased thickness of digits is referred to as acromegaly. Accompanying problems can include pressure on nerves (e.g., carpal tunnel syndrome), muscle weakness, insulin resistance or even a rare form of type 2 diabetes, and reduced sexual function.
- GH-secreting tumors are typically recognized in the 5th decade of life. It is extremely rare for such a tumor to occur in childhood, but when it does the excessive GH can cause excessive growth, traditionally referred to as pituitary gigantism.
- Surgical removal is the usual treatment for GH-producing tumors. In some circumstances focused radiation or a GH antagonist such as bromocriptine or octreotide may be employed to shrink the tumor or block function.

**B) Growth hormone deficiency (GHD)**

- Deficiency of GH produces significantly different problems at various ages. In children, growth failure and short stature are the major manifestations of GH deficiency. In adults the effects of deficiency are more subtle, and may include deficiencies of strength, energy, and bone mass, as well as increased cardiovascular risk.
- There are many causes of GH deficiency, including mutations of specific genes, congenital malformations involving the hypothalamus and/or pituitary gland, and damage to the pituitary from injury, surgery or disease.
- Diagnosis of GH deficiency involves a multiple step diagnostic process, usually culminating in GH stimulation test(s) to see if the patient's pituitary gland will release a pulse of GH when provoked by various stimuli.
- GH deficiency is treated by replacing GH. All GH in current use is a biosynthetic version of human GH, manufactured by recombinant DNA technology. As GH is a large protein molecule, it must be injected into subcutaneous tissue (or muscle) to get it into the blood. When the patient has had a long-standing deficiency of GH, benefits of treatment are often dramatic and gratifying and side effects of treatment are rare. Increased growth in childhood can result in dramatically improved adult height.
- GH is used as replacement therapy in adults with GH deficiency of either childhood-onset (after completing growth phase) or adult-onset (usually as a result of an acquired pituitary tumor). In these patients, benefits have variably included reduced fat mass, increased lean mass, increased bone density, improved lipid profile, reduced cardiovascular risk factors, and improved psychosocial well-being.
- This topic is treated more fully in the articles growth hormone deficiency and growth hormone treatment

**2.2.1-2. Prolactin Hormone & its functions:**

- Prolactin is a single chain polypeptide of 199 amino acids with a molecular weight of about 24,000 daltons. Prolactin is synthesised and secreted by **lactotrope** cells in the adenohypophysis (anterior pituitary gland). It is also produced in other tissues including the breast and the decidua.
- Pituitary prolactin secretion is regulated by neuroendocrine neurons in the hypothalamus, most importantly by neurosecretory dopamine neurons of the arcuate nucleus, which inhibit prolactin secretion. Thyrotropin-releasing factor has a stimulatory effect on prolactin release.
- Vasoactive intestinal peptide and peptide histidine isoleucine help to regulate prolactin secretion in humans, but the functions of these hormones in birds can be quite different

- Prolactin has many functions:
  - The most important of which is to stimulate the mammary glands to produce milk (lactation). Increased serum concentrations of prolactin during pregnancy cause enlargement of the mammary glands of the breasts and increases the production of milk. However, the high levels of progesterone during pregnancy act directly on the breasts to stop ejection of milk. It is only when the levels of this hormone fall after childbirth that milk ejection is possible. Sometimes, newborn babies (males as well as females) secrete a milky substance from their nipples. This substance is commonly known as Witch's milk. This is caused by the fetus being affected by prolactin circulating in the mother just before birth, and usually stops soon after birth.
  - Another effect, recently discovered by the University of Paisley and the Technische Hochschule Zürich, is to provide the body with sexual gratification after sexual acts. The hormone represses the effect of dopamine, which is responsible for sexual arousal, thus causing the male's refractory period. The amount of prolactin can be an indicator for the amount of sexual satisfaction and relaxation. Unusually high amounts are suspected to be responsible for impotence and loss of libido.
  - Prolactin has been found to stimulate proliferation of oligodendrocyte precursor cells. These cells differentiate into oligodendrocytes, the cells responsible for the formation of myelin coatings on axons in the central nervous system.

### **Clinical Problems**

- During pregnancy, high circulating concentrations of estrogen promote prolactin production. The resulting high levels of prolactin secretion cause further maturation of the mammary glands, preparing them for lactation.
- After childbirth, prolactin levels fall as the internal stimulus for them is removed. Sucking by the baby on the nipple then promotes further prolactin release, maintaining the ability to lactate. The sucking activates mechanoreceptors in and around the nipple. These signals are carried by nerve fibres through the spinal cord to the hypothalamus, where changes in the electrical activity of neurons that regulate the pituitary gland cause increased prolactin secretion. The suckling stimulus also triggers the release of oxytocin from the posterior pituitary gland, which triggers milk let-down: prolactin controls milk production (lactogenesis) but not the milk-ejection reflex; the rise in prolactin fills the breast with milk in preparation for the next feed.
- Usually, in the absence of galactorrhea, lactation will cease within one or two weeks of the end of demand breastfeeding.
- High prolactin levels also tend to suppress the ovulatory cycle by inhibiting the secretion of both FSH and GnRH.

- Prolactin levels may be checked as part of a sex hormone workup, as elevated prolactin secretion can suppress the secretion of FSH and GnRH, leading to hypogonadism, and sometimes causing erectile dysfunction in men.
- Prolactin levels may be of some use in distinguishing epileptic seizures from psychogenic non-epileptic seizures. The serum prolactin level usually rises following an epileptic seizure.

#### **A) Conditions causing elevated prolactin secretion**

- Hyperprolactinaemia is the term given to having too-high levels of prolactin in the blood.
- Prolactinoma;
- Excess thyrotropin-releasing hormone (TRH), usually in primary hypothyroidism.
- A side effect of many anti-psychotic medications

#### **B) Conditions causing decreased prolactin**

- Bulimia;
- Excess of dopamine.

### **2.2.1-3. Follicle Stimulating Hormone (FSH)**

- **Follicle stimulating hormone (FSH)** is a hormone synthesised and secreted by gonadotropes in the anterior pituitary gland. In the ovary FSH stimulates the growth of immature Graafian follicles to maturation. As the follicle grows it releases inhibin, which shuts off the FSH production. In men, FSH enhances the production of androgen-binding protein by the Sertoli cells of the testes and is critical for spermatogenesis. FSH and LH act synergistically in reproduction.
- FSH is a glycoprotein. Each monomeric unit is a protein molecule with a sugar attached to it; two of these make the full, functional protein. Its structure is similar to LH, TSH, and hCG. The protein dimer contains 2 polypeptide units, labelled alpha and beta subunits. The alpha subunits of LH, FSH, TSH, and hCG are identical, and contain 92 amino acids. The beta subunits vary. FSH has a beta subunit of 118 amino acids (FSHB) that confers its specific biologic action and is responsible for interaction with the FSH-receptor. The sugar part of the hormone is composed of fructose, galactose, mannose, galactosamine, glucosamine, and sialic acid, the latter being critical for its biologic half-life. The half-life of FSH is 3-4 hours.
- In both males and females, FSH stimulates the maturation of germ cells. In females, FSH initiates follicular growth, specifically affecting granulosa cells. With the concomitant rise in inhibin beta FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to ovulation. At the end of the luteal phase, there is a slight rise in FSH that seems to be of importance to start the next ovulatory cycle.

- Like its partner, LH, FSH release at the pituitary gland is controlled by pulses of gonadotropin-releasing hormone (GnRH). Those pulses, in turn, are subject to the estrogen feed-back from the gonads.
- FSH levels are normally low during childhood and, in women, high after menopause.
- High levels of Follicle Stimulating Hormone are indicative of situations where the normal restricting feedback from the gonad is absent, leading to an unrestricted pituitary FSH production. While this is typical in the menopause, it is abnormal in the reproductive years.

### ***Clinical problems:***

- Diminished secretion of FSH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, cessation of reproductive cycles is commonly observed. Conditions with very low FSH secretions are:
  1. Kallmann syndrome
  2. Hypothalamic suppression
  3. Hypopituitarism
  4. Hyperprolactinemia
  5. Gonadotropin deficiency
  6. Gonadal suppression therapy

### **2.2.1-4 Luteinizing hormone (LH)**

- **Luteinizing hormone (LH)**, also known as **lutropin** is a hormone synthesized and secreted by gonadotropes in the anterior lobe of the pituitary gland. In concert with the other pituitary gonadotropin follicle stimulating hormone (FSH) it is necessary for proper reproductive function:
  - In the *female*, an acute rise of LH – the *LH surge* – triggers ovulation.
  - In the *male*, where LH had also been called **Interstitial Cell Stimulating Hormone (ICSH)**, it stimulates Leydig cell production of testosterone
- LH is a glycoprotein. Each monomeric unit is a protein molecule with a sugar attached to it; two of these make the full, functional protein.
- Its structure is similar to the other glycoproteins, FSH, TSH, and hCG. The protein dimer contains 2 polypeptide units, labeled alpha and beta subunits that are connected by two disulfide bridges.
- The *alpha subunits* of LH, FSH, TSH, and hCG are identical, and contain 92 amino acids.
- The *beta subunits* vary. LH has a beta subunit of 121 amino acids (LHB) that confers its specific biologic action and is responsible for interaction with the LH receptor. This beta subunit contains the same amino acids in sequence as the beta

sub unit of hCG and both stimulate the same receptor, however, the hCG beta subunit contains an additional 24 amino acids, and both hormones differ in the composition of their sugar moieties.

- The different composition of these oligosaccharides affects bioactivity and speed of degradation. The biologic half-life of LH is 20 minutes, shorter than that of FSH (3-4 hours) or hCG (24 hours).
- In both males and females, LH is essential for reproduction.
  - **In females**, at the time of menstruation, FSH initiates follicular growth, specifically affecting granulosa cells. With the rise in estrogens, LH receptors are also expressed on the maturing follicle that produces an increasing amount of estradiol. Eventually at the time of the maturation of the follicle, the estrogen rise leads via the hypothalamic interface to the "positive feed-back" effect, a release of LH over a 24-48 hour period. This 'LH surge' triggers ovulation hereby not only releasing the egg, but also initiating the conversion of the residual follicle into a corpus luteum that, in turn, produces progesterone to prepare the endometrium for a possible implantation. LH is necessary to maintain luteal function for the first two weeks. In case of a pregnancy luteal function will be further maintained by the action of hCG from the newly established pregnancy. LH supports thecal cells in the ovary that provide androgens and hormonal precursors for estradiol production.
  - **In the male**, LH acts upon the Leydig cell of the testis and is responsible for the production of testosterone, the "male hormone" that exerts both endocrine activity and intratesticular activity such as spermatogenesis.
- The release of LH at the pituitary gland is controlled by pulses of gonadotropin-releasing hormone (GnRH) from the hypothalamus.

### **Clinical problems**

- LH levels are normally low during childhood and, in women, high after menopause.
- During the reproductive years typical levels are between 5-20 mIU/ml.
- Physiologic high LH levels are seen during the LH surge (v.s.); typically they last 48 hours.

#### **A) Relative elevations**

- In children with precocious puberty of pituitary or central origin, LH and FSH levels may be in the reproductive range instead of the low levels typical for their age.
- During the reproductive years, relatively elevated LH is frequently seen in patients with the polycystic ovary syndrome; however it would be unusual for them to have LH levels outside of the normal reproductive range.

#### **B) High LH levels**

- Persistently high LH levels are indicative of situations where the normal restricting feedback from the gonad is absent, leading to an unrestricted pituitary production of both LH and FSH. While this is typical in the menopause, it is abnormal in the reproductive years. There it may be a sign of:
  1. Premature menopause
  2. Gonadal dysgenesis, Turner syndrome
  3. Castration
  4. Swyer syndrome
  5. Certain forms of CAH
  6. Testicular failure

### **C) Deficient LH activity**

- Diminished secretion of LH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, amenorrhea is commonly observed. Conditions with very low LH secretions are:
  1. Kallmann syndrome
  2. Hypothalamic suppression
  3. Hypopituitarism
  4. Eating disorder
  5. Hyperprolactinemia
  6. Gonadotropin deficiency
  7. Gonadal suppression therapy

## **2.2.1-5 Thyroid Stimulating Hormone (TSH)**

- **Thyroid-stimulating hormone** (also known as **TSH** or **thyrotropin**) is a hormone synthesized and secreted by thyrotrope cells in the anterior pituitary gland which regulates the endocrine function of the thyroid gland.
- TSH stimulates the thyroid gland to secrete the hormones thyroxine (T<sub>4</sub>) and triiodothyronine (T<sub>3</sub>). TSH production is controlled by a Thyrotropin Releasing Hormone, (TRH), which is manufactured in the hypothalamus and transported to the Anterior Pituitary gland, where it increases TSH production and release. Somatostatin is also produced by the hypothalamus, and has an opposite effect on the pituitary production of TSH, decreasing or inhibiting its release.
- The level of Thyroid hormones (T<sub>3</sub>, T<sub>4</sub> and T<sub>5</sub>) in the blood have an additional effect on the pituitary release of TSH, When the levels of T<sub>3</sub> and T<sub>4</sub> are low, the production of TSH is increased, and conversely, when levels of T<sub>3</sub> and T<sub>4</sub> are high, then TSH production is decreased. This effect creates a regulatory negative feedback loop.
- TSH is a glycoprotein and consists of two subunits, the *alpha* and the *beta* subunit.
  - The  $\alpha$  (*alpha*) subunit is identical to that of human chorionic gonadotropin (HCG), luteinising hormone (LH), follicle-stimulating hormone (FSH).

- The  $\beta$  (beta) subunit is unique to TSH, and therefore determines its function.
- The TSH receptor is found mainly on thyroid follicular cells. Stimulation of the receptor increases T3 and T4 production and secretion.
- Stimulating antibodies to this receptor mimic TSH action and are found in Graves' disease.

### **Clinical problems**

- TSH levels are tested in the blood of patients suspected of suffering from excess (hyperthyroidism), or deficiency (hypothyroidism) of thyroid hormone. Generally, a normal range for TSH is between 0.3 and 3.0 uIU/mL (equivalent to mIU/L), but the interpretation depends also on what the blood levels of thyroid hormones (T3 and T4) are.

**Table: 2 Clinical problems due to thyroid hormones**

Source of pathology	TSH level	thyroid hormone level	Disease causing conditions
hypothalamus/pituitary	High	high	benign tumor of the pituitary (adenoma) or thyroid hormone resistance
hypothalamus/pituitary	Low	low	hypopituitarism
thyroid	Low	high	hyperthyroidism or Grave's disease
thyroid	High	low	congenital hypothyroidism (cretinism), hypothyroidism

- Clearly, both TSH and T3 and T4 should be measured to ascertain where a specific thyroid dysfunction is caused by primary pituitary or by a primary thyroid disease. If both are up (or down) then the problem is probably in the pituitary. If the one component (TSH) is up, and the other (T3 and T4) is down, then the disease is probably in the thyroid itself. The same holds for a low TSH, high T3 and T4 finding.

### **2.2.1-6. Adreno Cortico Tropic Hormone (ACTH)**

- **Adrenocorticotrophic hormone (ACTH or corticotropin)** is a peptide hormone produced and secreted by the hypothalamus. It is an important player in the hypothalamic-pituitary-adrenal axis.
- ACTH synthesised from pro-opiomelanocortin (POMC) and secreted from corticotropes in the anterior lobe of the pituitary gland in response to the hormone corticotropin-releasing hormone (CRH) released by the hypothalamus
- ACTH consists of 39 amino acids, the first 13 of which (counting from the N-terminus) may be cleaved to form  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH).

(This common structure is one reason that patients with hypercortisolism, in which ACTH levels are elevated, often present with excessively tanned skin.)

- Together with ACTH, the hormones lipotropin, melanocyte-stimulating hormone (MSH),  $\beta$ -endorphin and met-enkephalin are also released.
- ACTH acts through the stimulation of cell surface ACTH receptors, which are primarily located on the adrenocortical cells. ACTH stimulates the cortex of the adrenal gland and boosts the synthesis of corticosteroids, mainly glucocorticoids but also mineralcorticoids and sex steroids (androgens).
- ACTH is also related to the circadian rhythm in many organisms. The half-life of ACTH in human blood is about 10 minutes

### **Clinical problems**

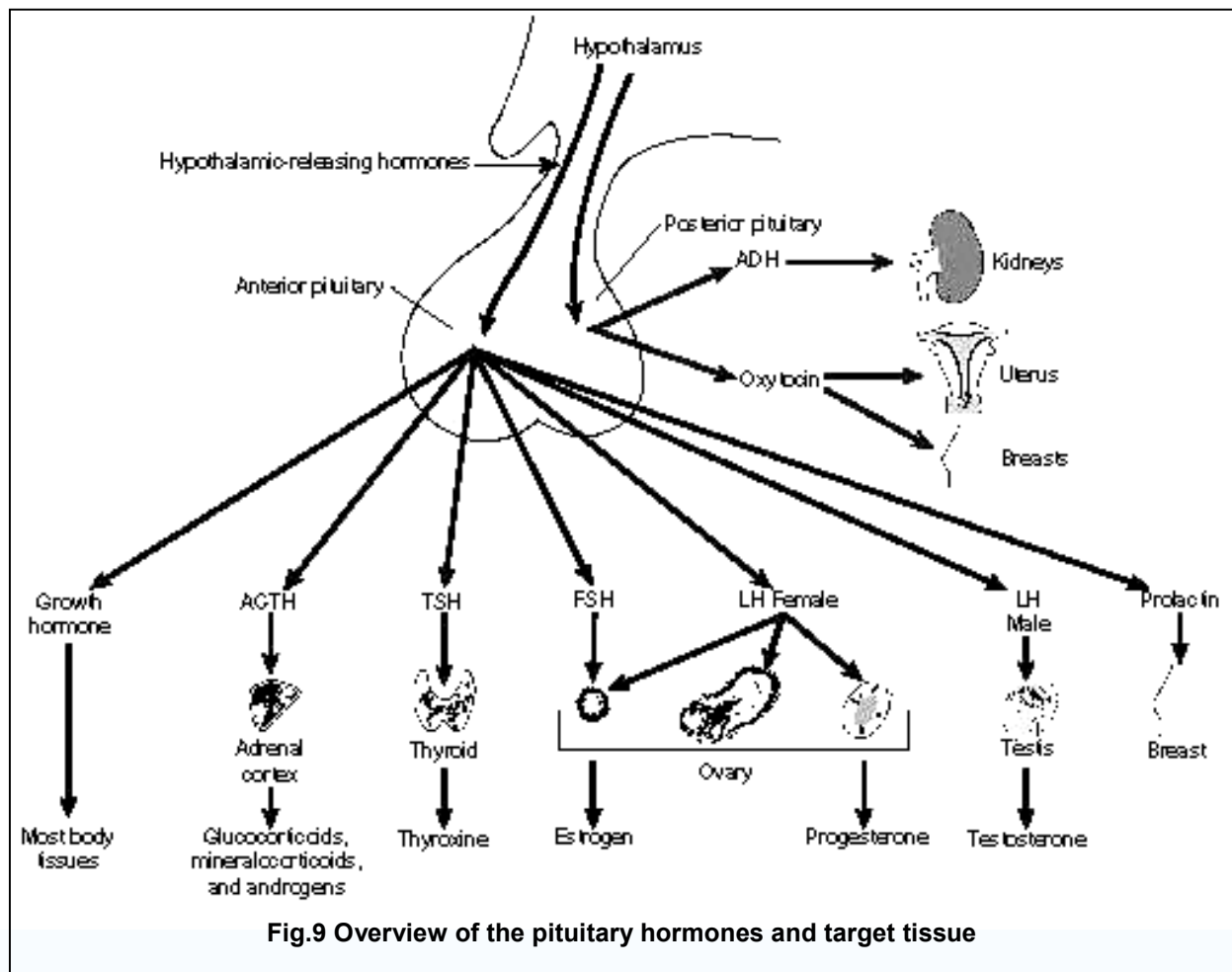
The following are the associated conditions to ACTH

- Addison's disease
- Small cell carcinoma
- adrenoleukodystrophy
- Congenital adrenal hyperplasia
- Cushing's syndrome
- Nelson's syndrome

### **2.2.1-7. Endorphins**

- Endorphins (or more correctly Endomorphines) are endogenous opioid biochemical compounds. They are peptides produced by the pituitary gland and the hypothalamus in vertebrates, and they resemble the opiates in their abilities to produce analgesia and a sense of well-being. In other words, they might work as "natural pain killers." Using drugs may increase the effects of the endorphins.
- The term "endorphin" implies a pharmacological activity (analogous to the activity of the corticosteroid category of biochemicals) as opposed to a specific chemical formulation.
- Scientists debate whether specific activities release measurable levels of endorphins. Much of the current data comes from animal models which may not be relevant to humans. The studies that do involve humans often measure endorphin plasma levels, which do not necessarily correlate with levels in the CNS. Other studies use an opioid antagonist, usually naloxone, to indirectly measure the release of endorphins by observing the changes that occur when any endorphin activity that might be present is blocked.
- Capsaicin (the active chemical in chili peppers) also has been shown to stimulate endorphin release. Topical capsaicin has been used as a treatment for certain types of chronic pain.

- In 1999, clinical researchers reported that inserting acupuncture needles into specific body points triggers the production of endorphins. In another study, higher levels of endorphins were found in cerebrospinal fluid after patients underwent acupuncture. In addition, naloxone appeared to block acupuncture's pain-relieving effects. However, skeptics say that not all studies point to that conclusion, and that in a trial of chronic pain patients, endorphins did not produce long-lasting relief.



### 2.2.2 HORMONES OF NEUROHYPOPHYSIS

- The hormones secreted by the posterior pituitary are:
  - Oxytocin comes from the paraventricular nucleus in the Hypothalamus
  - Antidiuretic hormone (ADH - also known as vasopressin and AVP, arginine vasopressin), comes from the supraoptic nucleus in the Hypothalamus.

#### 2.2.2-1 Oxytocin

- **Oxytocin** (Greek: "quick birth") is a mammalian hormone that also acts as a neurotransmitter in the brain. In women, it is released mainly after distension of the cervix and vagina during labor, and after stimulation of the nipples, facilitating birth and breastfeeding, respectively. Oxytocin is released during orgasm in both sexes. In the brain, oxytocin is involved in social recognition and bonding, and might be involved in the formation of trust between people.
- Oxytocin is made in magnocellular neurosecretory cells in the supraoptic nucleus and paraventricular nucleus of the hypothalamus and is released into the blood from the posterior lobe of the pituitary gland. Oxytocin is also made by some neurons in the paraventricular nucleus that project to other parts of the brain and to the spinal cord.
- In the pituitary gland, oxytocin is packaged in large, dense-core vesicles, where it is bound to neurophysin as shown in the inset of the figure; neurophysin is a large peptide fragment of the giant precursor protein molecule from which oxytocin is derived by enzymatic cleavage.
- Secretion of oxytocin from the neurosecretory nerve endings is regulated by the electrical activity of the oxytocin cells in the hypothalamus. These cells generate action potentials that propagate down axons to the nerve endings in the pituitary; the endings contain large numbers of oxytocin-containing vesicles, which are released by exocytosis when the nerve terminals are depolarised.
- Oxytocin is a peptide of nine amino acids (a nonapeptide). The sequence is cysteine - tyrosine - isoleucine - glutamine - asparagine - cysteine - proline - leucine - glycine (CYIQNCPLG). The cysteine residues form a sulfur bridge. Oxytocin has a molecular mass of 1007 daltons. One international unit (IU) of oxytocin is the equivalent of about 2 micrograms of pure peptide.
- The structure of oxytocin is very similar to that of vasopressin (cysteine - tyrosine - phenylalanine - glutamine - asparagine - cysteine - proline - arginine - glycine), also a nonapeptide with a sulfur bridge whose sequence differs from oxytocin by 2 amino acids. A table showing the sequences of members of the vasopressin/oxytocin superfamily and the species expressing them is present in the vasopressin article. Oxytocin and vasopressin were discovered, isolated and synthesized by Vincent du Vigneaud in 1953, work for which he received the Nobel Prize in Chemistry in 1955.
- Oxytocin and vasopressin are the only known hormones released by the human posterior pituitary gland to act at a distance. However, oxytocin neurons make other peptides, including corticotropin-releasing hormone (CRH) and dynorphin, for example, that act locally. The magnocellular neurons that make oxytocin are adjacent to magnocellular neurons that make vasopressin, and are similar in many respects.

### **Functions of Oxytocin**

- Oxytocin has peripheral (hormonal) actions, and also has actions in the brain. The actions of oxytocin are mediated by specific, high affinity oxytocin receptors. The

oxytocin receptor is a G-protein-coupled receptor which requires  $Mg^{2+}$  and cholesterol. It belongs to the rhodopsin-type (class I) group of G-protein-coupled receptors.

### **A) Peripheral (hormonal) actions**

- The peripheral actions of oxytocin mainly reflect secretion from the pituitary gland. (See oxytocin receptor for more detail on its action.)
- Letdown reflex – in lactating (breastfeeding) mothers, oxytocin acts at the mammary glands, causing milk to be 'let down' into a collecting chamber, from where it can be extracted by sucking at the nipple. Sucking by the infant at the nipple is relayed by spinal nerves to the hypothalamus. The stimulation causes neurons that make oxytocin to fire action potentials in intermittent bursts; these bursts result in the secretion of pulses of oxytocin from the neurosecretory nerve terminals of the pituitary gland.
- Uterine contraction – important for cervical dilation before birth and causes contractions during the second and third stages of labor. Oxytocin release during breastfeeding causes mild but often painful uterine contractions during the first few weeks of lactation. This also serves to assist the uterus in clotting the placental attachment point postpartum. However, in knockout mice lacking the oxytocin receptor, reproductive behavior and parturition is normal.
- Oxytocin is secreted into the blood at orgasm – in both males and females. In males, oxytocin may facilitate sperm transport in ejaculation.
- Due to its similarity to vasopressin, it can reduce the excretion of urine slightly. More important, in several species, oxytocin can stimulate sodium excretion from the kidneys (natriuresis), and in humans, high doses of oxytocin can result in hyponatremia.
- Oxytocin and oxytocin receptors are also found in the heart in some rodents, and the hormone may play a role in the embryonal development of the heart by promoting cardiomyocyte differentiation. However, the absence of either oxytocin or its receptor in knockout mice has not been reported to produce cardiac insufficiencies.

### **B) Actions of oxytocin within the brain**

- Oxytocin secreted from the pituitary gland cannot re-enter the brain because of the blood-brain barrier. Instead, the behavioral effects of oxytocin are thought to reflect release from centrally-projecting oxytocin neurons, different from those that project to the pituitary gland. Oxytocin receptors are expressed by neurons in many parts of the brain and spinal cord.
- Sexual arousal. Oxytocin injected into the cerebrospinal fluid causes spontaneous erections in rats, reflecting actions in the hypothalamus and spinal cord.

- **Bonding.** In the Prairie Vole, oxytocin released into the brain of the female during sexual activity is important for forming a monogamous pair bond with her sexual partner. Vasopressin appears to have a similar effect in males<sup>[6]</sup>. In people, plasma concentrations of oxytocin have been reported to be higher amongst people who claim to be falling in love. Oxytocin has a role in social behaviors in many species, and so it seems likely that it has similar roles in humans. It has been suggested that deficiencies in oxytocin pathways in the brain might be a feature of autism.
- **Maternal behavior.** Sheep and rat females given oxytocin antagonists after giving birth do not exhibit typical maternal behavior. By contrast, virgin sheep females show maternal behavior towards foreign lambs upon cerebrospinal fluid infusion of oxytocin, which they would not do otherwise.
- **Various anti-stress functions.** Oxytocin reduces blood pressure and cortisol levels, increasing tolerance to pain, and reducing anxiety. Oxytocin may play a role in encouraging "tend and befriend", as opposed to "fight or flight", behavior, in response to stress.
- **Increasing trust and reducing fear.** In a risky investment game, experimental subjects given nasally administered oxytocin displayed "the highest level of trust" twice as often as the control group. Subjects who were told that they were interacting with a computer showed no such reaction, leading to the conclusion that oxytocin was not merely affecting risk-aversion. Nasally-administered oxytocin has also been reported to reduce fear, possibly by inhibiting the amygdala (which is thought to be responsible for fear responses). There is no conclusive evidence for access of oxytocin to the brain through intranasal administration, however.
- **According to some studies in animals,** oxytocin inhibits the development of tolerance to various addictive drugs (opiates, cocaine, alcohol) and reduces withdrawal symptoms.
- **Preparing fetal neurons to delivery.** Crossing placenta, maternal oxytocin reaches fetal brain and induces a switch in the action of neurotransmitter GABA from excitatory to inhibitory on fetal cortical neurons. This silences fetal brain for the period of delivery and reduces its vulnerability to hypoxic damage.
- **Certain learning and memory functions are impaired by centrally-administered oxytocin.**

### ***Clinical problems:***

- Oxytocin is relatively safe when used at recommended doses. Potential side effects include:
  - **Central nervous system:** Subarachnoid hemorrhage, seizures.
  - **Cardiovascular:** Increased heart rate, blood pressure, systemic venous return, cardiac output, and arrhythmias.

- Genitourinary: Impaired uterine blood flow, pelvic hematoma, tetanic uterine contractions, uterine rupture, postpartum hemorrhage.

### 2.2.2-2 Vasopressin Hormone & its functions

- **Arginine vasopressin (AVP)**, also known as **argipressin** or **antidiuretic hormone (ADH)**, is a human hormone that is mainly released when the body is low on water; it causes the kidneys to conserve water by concentrating the urine and reducing urine volume. It also has various functions in the brain and blood vessels.
- The vasopressins are peptides consisting of nine amino acids (nonapeptides). (NB: the value in the table above of 164 amino acids is that obtained before the hormone is activated by cleavage). The amino acid sequence of arginine vasopressin is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly, with the cysteine residues forming a sulfur bridge. Lysine vasopressin has a lysine in place of the arginine.
- A very similar substance, **lysine vasopressin (LVP)** or **lypressin**, has the same function in pigs and is often used in human therapy.
- Vasopressin is a **peptide hormone** liberated from a preprohormone precursor that is synthesized in the hypothalamus as it is transported to the posterior pituitary. Most of it is stored in the posterior part of the pituitary gland to be released into the blood stream; some of it is also released directly into the brain.
- The vasopressin that is measured in peripheral blood is almost all derived from secretion from the posterior pituitary gland (except in cases of vasopressin-secreting tumours). However there are two other sources of vasopressin with important local effects:
  - Vasopressin is secreted from parvocellular neurons of the paraventricular nucleus at the median eminence into the short portal vessels of the pituitary stalk. These vessels carry the peptide directly to the anterior pituitary gland, where it is an important releasing factor for ACTH, acting in conjunction with CRH.
  - Vasopressin is also released into the brain by several different populations of neurons

#### Functions

- Vasopressin released within the brain has many actions:
  - It has been implicated in memory formation, including delayed reflexes, image, short- and long-term memory, though the mechanism remains unknown, and these findings are controversial.
  - Vasopressin is released into the brain in a circadian rhythm by neurons of the suprachiasmatic nucleus of the hypothalamus.

- Vasopressin released from centrally-projecting hypothalamic neurons is involved in aggression, blood pressure regulation and temperature regulation.
- In recent years there has been particular interest in the role of vasopressin in social behavior. It is thought that vasopressin, released into the brain during sexual activity, initiates and sustains patterns of activity that support the pair-bond between the sexual partners; in particular, vasopressin seems to induce the male to become aggressive towards other males.
- Evidence for this comes from experimental studies, in several species, which indicate that the precise distribution of vasopressin and vasopressin receptors in the brain is associated with species-typical patterns of social behavior. In particular, there are consistent differences between monogamous species and promiscuous species in the distribution of vasopressin receptors, and sometimes in the distribution of vasopressin-containing axons, even when closely-related species are compared. Moreover, studies involving either injecting vasopressin agonists into the brain, or blocking the actions of vasopressin, support the hypothesis that vasopressin is involved in aggression towards other males.
- There is also evidence that differences in the vasopressin receptor gene between individual members of a species might be predictive of differences in social behavior.

Here is a **table:3** summarizing some of the actions of Avp at its three receptors, differently expressed in different tissues and exerting different actions:

Type	Second messenger system	Locations	Actions
AVPR1A	phosphatidylinositol/calcium	liver, kidney, peripheral vasculature, brain	vasoconstriction, gluconeogenesis, platelet aggregation, and release of factor VIII and von Willebrand factor; social recognition, circadian tau
AVPR1B	phosphatidylinositol/calcium	pituitary gland, brain	adrenocorticotrophic hormone secretion in response to stress; social interpretation to olfactory cues
AVPR2	adenylate cyclase/cAMP	apical membrane of the cells lining the collecting ducts of the kidneys (especially the cortical and outer medullary collecting ducts)	insertion of aquaporin-2 (AQP2) channels (water channels). This allows water to be reabsorbed down an osmotic gradient, and so the urine is more concentrated.

### **Clinical Problems**

- Decreased vasopressin release or decreased renal sensitivity to vasopressin leads to diabetes insipidus, a condition featuring hypernatremia (increased blood sodium content), polyuria (excess urine production), and polydipsia (thirst).
- High levels of vasopressin secretion (syndrome of inappropriate antidiuretic hormone, SIADH) and resultant hyponatremia (low blood sodium levels) occurs in brain diseases and conditions of the lungs. In the perioperative period, the effects of surgical stress and some commonly used medications (e.g., opiates, syntocinon, anti-emetics) lead to a similar state of excess vasopressin secretion. This may cause mild hyponatraemia for several days.

### **2.2.3. HORMONES OF MID LOBE PITUITARY**

- **Pars intermedia** is the boundary between the anterior and posterior lobes of the pituitary. It contains three types of cell - basophils, chromophobes, and colloid-filled cysts. The cysts are the remainder of Rathke's pouch.
- In human fetal life, this area produces melanocyte stimulating hormone or MSH which causes the release of melanin pigment in skin melanocytes (pigment cells). However, the pars intermedia is normally either very small or entirely absent in adulthood.

#### **2.2.3-1. MSH (Melanocyte Stimulating Hormone)**

- The **melanocyte-stimulating hormones** (collectively referred to as **MSH**) are a class of peptide hormones produced by cells in the intermediate lobe of the pituitary gland.
- Two synthetic analogs of alpha-MSH, based upon a peptide called Melanotan are being developed for human use, one by an Australian company the other by a New Jersey company.
- Alpha-MSH topical cream is being investigated as a possible therapeutic aid in the treatment of melanoma.
- An additional analog called Melanotan II causes enhanced libido and erections in most male test subject and arousal with corresponding genital involvement in most female test subjects. Bremelanotide (formerly PT-141) the peptide that is being developed by the New Jersey company is a close analog of melanotan II that shares its aphrodisiac effects and is currently in clinical trials to treat erectile dysfunction and sexual arousal disorder. These effects are mediated by actions in the hypothalamus on neurons that express MC3 MC3R and MC4 MC4R receptors

### **Functions & Clinical Problems:**

- They stimulate the production and release of melanin (melanogenesis) by melanocytes in skin and hair. MSH is also produced by a subpopulation of neurons

in the arcuate nucleus of the hypothalamus. MSH released into the brain by these neurons has effects on appetite and sexual arousal.

- **In amphibians**

- In some animals (such as the claw-toed frog *Xenopus laevis*) production of MSH is increased when the animal is in a dark location. This causes pigment to be dispersed in pigment cells in the toad's skin, making it become darker, and harder for predators to spot. The pigment cells are called melanophores and therefore, in amphibians, the hormone is often called melanophore-stimulating hormone.

- **In humans**

- An increase in MSH will cause a darkening in humans too. Melanocyte-stimulating hormone increases in humans during pregnancy. This, along with increased estrogens, causes increased pigmentation in pregnant women. In Addison's disease high levels of adrenocorticotrophic hormone (ACTH) production also leads to high MSH levels, which cause an abnormal darkening.
- Different levels of MSH are not the major cause of racial variation in skin colour. In many red headed people, and other people who do not tan well, there are variations in their hormone receptors, causing them to not respond to MSH in the blood.

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## 2.3. THYROID HORMONES

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- The **thyroid** (from the Greek word for "shield", after its shape) is one of the larger endocrine glands in the body. It is a double-lobed structure located in the neck and produces hormones, principally **thyroxine** ( $T_4$ ) and **triiodothyronine** ( $T_3$ ), that regulate the rate of metabolism and affect the growth and rate of function of many other systems in the body.
- **Iodine** is an essential component of both  $T_3$  and  $T_4$ . The thyroid also produces the hormone **calcitonin**, which plays a role in calcium homeostasis. Hyperthyroidism (overactive thyroid) and hypothyroidism (underactive thyroid) are the most common problems of the thyroid gland. Specialists are called Thyroidologists.

### 2.3.1 Thyroxine hormone & its functions

- The **thyroid hormones**, thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ), are tyrosine-based hormones produced by the thyroid gland. An important component in the synthesis is iodine. The major form of thyroid hormone in the blood is thyroxine ( $T_4$ ). The ratio of  $T_4$  to  $T_3$  released in the blood is roughly 20 to 1. Thyroxine is converted to the active  $T_3$  (three to four times more potent than  $T_4$ ) within cells by deiodinases (5'-iodinase). These are further processed by decarboxylation and deiodination to produce iodothyronamine ( $T_{1a}$ ) and thyronamine ( $T_{0a}$ ).

- Thyroxine (3,5,3',5'-tetraiodothyronine) is produced by follicular cells of the thyroid gland. It is produced as the precursor **thyroglobulin** (this is *not* the same as TBG), which is cleaved by enzymes to produce active T<sub>4</sub>.
- Thyroxine is produced by attaching iodine atoms to the ring structures of tyrosine molecules. Thyroxine contains four iodine atoms. Triiodothyronine is identical to T<sub>4</sub>, but it has one less iodine atom per molecule.
- Iodide is actively absorbed from the bloodstream and concentrated in the thyroid follicles. (If there is a deficiency of dietary iodine, the thyroid enlarges in an attempt to trap more iodine, resulting in goitre.) Via a reaction with the enzyme thyroperoxidase, iodine is covalently bound to tyrosine residues in the thyroglobulin molecules, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Linking two moieties of DIT produces thyroxine. Combining one particle of MIT and one particle of DIT produces triiodothyronine.
  - MIT + DIT = triiodothyronine (usually referred to as T<sub>3</sub>)
  - DIT + DIT = thyroxine (referred to as T<sub>4</sub>)
- Proteases digest iodinated thyroglobulin, releasing the hormones T<sub>4</sub> and T<sub>3</sub>, the biologically active agents central to metabolic regulation. Thyroxine is supposedly a prohormone and a reservoir for the most active and main thyroid hormone T<sub>3</sub>. T<sub>4</sub> is converted as required in the tissues by deiodinases. Deficiency of deiodinase can mimic as iodine deficiency. T<sub>3</sub> is more active than T<sub>4</sub> and is the final form of the hormone, though it is present in less quantity than T<sub>4</sub>.
- Most of the thyroid hormone circulating in the blood is bound to transport proteins. Only a very small fraction of the circulating hormone is free (unbound) and biologically active, hence measuring concentrations of free thyroid hormones is of great diagnostic value
- When thyroid hormone is bound, it is not active, so the amount of free T<sub>3</sub>/T<sub>4</sub> is what is important. For this reason, measuring total thyroxine in the blood can be misleading.

### **Functions of thyroxine**

- The thyronines act on the body to increase the basal metabolic rate, affect protein synthesis and increase the body's sensitivity to **catecholamines** (such as adrenaline) by permissiveness. The thyroid hormones are essential to proper development and differentiation of all cells of the human body. These hormones also regulate *protein, fat, and carbohydrate metabolism*, affecting how human cells use energetic compounds. Numerous physiological and pathological stimuli influence thyroid hormone synthesis.
- The thyronamines function via some unknown mechanism to inhibit neuronal activity; this plays an important role in the hibernation cycles of mammals. One effect of administering the thyronamines is a severe drop in body temperature.

**A) Effects of thyroxine**

- Increases cardiac output
- Increases heart rate
- Increases ventilation rate
- Increases basal metabolic rate
- Development of brain
- Thickens endometrium

**B) Clinical problems**

- Both excess and deficiency of thyroxine can cause disorders.
- Thyrotoxicosis or **hyperthyroidism** (more specifically Graves Disease) is the clinical syndrome caused by an excess of circulating free thyroxine, free triiodothyronine, or both. It is a common disorder that affects approximately 2% of women and 0.2% of men.
- **Hypothyroidism** (an example is Hashimoto's thyroiditis) is the case where there is a deficiency of thyroxine, triiodothyronine, or both.
- **Clinical depression** can sometimes be caused by hypothyroidism. Some research has shown that  $T_3$  is found in the junctions of synapses, and regulates the amounts and activity of serotonin, norepinephrine, and Gamma-aminobutyric acid (GABA) in the brain.

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**2.3.2. Calcitonin Hormone & its function**

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- **Calcitonin** is a 32 amino acid polypeptide hormone that is produced in humans primarily by the C cells of the thyroid, and in many other animals in the ultimobranchial body
- It has found in fish, reptiles, birds and mammals. Its importance in humans has not been as well established as its importance in other animals.
- It is formed by proteolytic cleavage of a larger prepropeptide which is the product of the CALC1 gene (*CALCA*), which itself is part of a superfamily of related protein hormone precursors including Islet amyloid precursor protein, Calcitonin gene-related peptide and the precursor of Adrenomedullin.
- The hormone participates in calcium ( $Ca^{2+}$ ) and phosphorus metabolism. In many ways, calcitonin has the counter effects of parathyroid hormone (PTH).
- Specifically, calcitonin reduces blood  $Ca^{2+}$  levels in three ways:
  - Decreasing  $Ca^{2+}$  absorption by the intestines
  - Decreasing osteoclast activity in bones
  - Decreasing  $Ca^{2+}$  and phosphate reabsorption by the kidney tubules

**Functions of calcitonin:**

- Calcitonin and Its actions, broadly, are:
  - Bone mineral metabolism
    - Prevent postprandial hypercalcemia resulting from absorption of  $\text{Ca}^{2+}$  from foods during a meal
    - Promote mineralization of skeletal bone
    - Protect against  $\text{Ca}^{2+}$  loss from skeleton during periods of  $\text{Ca}^{2+}$  stress such as pregnancy and lactation
  - Vitamin D regulation
  - A satiety hormone
    - Inhibit food intake in rats and monkeys
    - May have CNS action involving the regulation of feeding and appetite
  - Salmon calcitonin is used for the treatment of:
    - Postmenopausal osteoporosis
    - Hypercalcaemia
    - Paget's disease
    - Bone metastases
    - Phantom limb pain

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## 2.4 PARATHYROID HORMONES

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- The **parathyroid glands** are small endocrine glands in the neck, usually located behind the thyroid gland, which produce parathyroid hormone. In rare cases the parathyroid glands are located within the thyroid glands. Most often there are four parathyroid glands but some people have six or even eight.

### 2.4.1 Parathyroid Hormones & its functions

- **Parathyroid hormone (PTH)**, or parathormone, is secreted by the parathyroid glands as a polypeptide containing 84 amino acids. It acts to increase the concentration of calcium in the blood, whereas calcitonin (a hormone produced by the thyroid gland) acts to decrease calcium concentration.
- PTH can be measured in the blood in several different forms: intact PTH; N-terminal PTH; mid-molecule PTH, and C-terminal PTH, and different tests are used in different clinical situations.

### **Functions of Parathyroid hormone:**

#### **A) Effects on serum calcium (raising)**

- PTH acts to increase the concentration of calcium in the blood by acting upon *parathyroid hormone receptor* in three parts of the body:

Table:4 Function of PTH

Region	Effect
bones	It enhances the release of calcium from the large reservoir contained in the bones. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH. Stimulation is indirect since osteoclasts do not have a receptor for PTH; rather, PTH binds to osteoblasts, the cells responsible for creating bone. Binding stimulates osteoblasts to increase their expression of RANKL, which can bind to osteoclast precursors containing RANK, a receptor for RANKL. The binding of RANKL to RANK stimulates these precursors to fuse, forming new osteoclasts which ultimately enhances the resorption of bone.
kidney	It enhances reabsorption of calcium from distal tubules.
intestine	It enhances the absorption of calcium in the intestine by increasing the production of vitamin D and upregulating the enzyme responsible for 1-alpha hydroxylation of 25-hydroxy vitamin D, converting vitamin D to its active form (1,25-dihydroxy vitamin D) which effects the actual absorption of calcium by the intestine.

### **B) Effects on serum phosphate (decrease, with compensation)**

- PTH reduces the uptake of phosphate in the proximal tubules of the kidney, which means more phosphate is excreted through the urine.
- However, PTH also enhances the uptake of phosphate from the intestine and bones into the blood. These responses to PTH cancel each other out, so the serum concentration of phosphate remains approximately the same.

### **C) Feedback regulation**

- Increased calcium concentration in the blood acts (via feedback inhibition) to decrease PTH secretion by the parathyroid glands.
- This is achieved by the activation of calcium-sensing receptors located on parathyroid cells.

### **Clinical Problems:**

- A high level of PTH in the blood is known as **hyperparathyroidism**.
  - If the cause is in the parathyroid gland it is called *primary hyperparathyroidism*. The causes are parathyroid adenoma, parathyroid hyperplasia and parathyroid cancer.
  - If the cause is outside the gland, it is known as *secondary hyperparathyroidism*. This can occur in chronic renal failure.

- A low level of PTH in the blood is known as hypoparathyroidism. Causes include surgical misadventure (eg inadvertent removal during routine thyroid surgery), autoimmune disorder, and **inborn errors of metabolism**.

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## 2.5 ADRENAL HORMONES

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- In mammals, the **adrenal gland** (also known as **suprarenal glands**) are the triangle-shaped endocrine glands that sit atop the kidneys; their name indicates that position (*ad*, "near" or "at" + *renes*, "kidneys"). They are chiefly responsible for regulating the stress response through the synthesis of corticosteroids and catecholamines, including cortisol and adrenaline.
- It is separated into two distinct structures, 1. Adrenal Medulla and 2. Adrenal Cortex
- The adrenal medulla is the central core of the adrenal gland, surrounded by the adrenal cortex. The chromaffin cells of the medulla are the body's main source of the catecholamine hormones **adrenaline** (epinephrine) and **noradrenaline** (norepinephrine).
- The adrenal cortex is devoted to synthesis of steroid hormones from cholesterol. Some cells belong to the hypothalamic-pituitary-adrenal axis and are the source of cortisol synthesis. Other cortical cells produce androgens such as testosterone, while some regulate water and electrolyte concentrations by secreting aldosterone.

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### 2.5.1 Adrenal Medullary Hormones

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- The **adrenal medulla** is part of the adrenal gland. It is located at the center of the gland, being surrounded by the adrenal cortex.
- Composed mainly of hormone-producing chromaffin cells, the adrenal medulla is the principal site of the conversion of the amino acid tyrosine into the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine).

#### 2.5.1-1. Adrenaline Hormone:

- **Epinephrine** or **adrenaline** sometimes spelled "epinephrin" or "adrenalin" respectively, is a hormone. It is a catecholamine, a sympathomimetic monoamine derived from the amino acids phenylalanine and tyrosine.
- Epinephrine is synthesized from norepinephrine in a synthetic pathway shared by all catecholamines, including L-dopa, dopamine, norepinephrine, and epinephrine.
- Epinephrine is synthesized from norepinephrine by phenylethanolamine N-methyltransferase (PNMT) in the cytosol of adrenergic neurons and cells of the adrenal medulla (so-called chromaffin cells). PNMT is only found in the cytosol of cells of adrenal medullary cells. PNMT uses S-adenosylmethionine (SAdMe) as a cofactor to donate the methyl group to norepinephrine, creating epinephrine.
- For norepinephrine to be acted upon by PNMT in the cytosol, it must first be shipped out of granules of the chromaffin cells. This may occur via the

catecholamine-H<sup>+</sup> exchanger VMAT1. VMAT1 is also responsible for transporting newly synthesized epinephrine from the cytosol back into chromaffin granules in preparation for release.

### **Functions of Adrenaline Hormone:**

- Epinephrine is a "fight or flight" hormone which is released from the adrenal glands whenever danger threatens. When secreted it floods out the endocrine gland into the bloodstream to instantly prepare the body for action in emergency situations. The hormone boosts the supply of oxygen and energy-giving glucose to the muscles making the individual more mentally alert and physically strong; only vital bodily processes occur.
- Epinephrine plays a central role in the short-term stress reaction—the physiological response to threatening, exciting, or environmental stressor conditions such as high noise levels or bright light. It is secreted by the adrenal medulla. When released into the bloodstream, epinephrine binds to multiple receptors and has numerous effects throughout the body. It increases heart rate and stroke volume, dilates the pupils, and constricts arterioles in the skin and gut while dilating arterioles in leg muscles. It elevates the blood sugar level by increasing catalysis of glycogen to glucose in the liver, and at the same time begins the breakdown of lipids in fat cells. Like some other stress hormones, epinephrine has a suppressive effect on the immune system.
- Epinephrine is used as a drug to increase peripheral resistance via alpha-stimulated **vasoconstriction** in cardiac arrest and other cardiac dysrhythmias resulting in diminished or absent cardiac output, such that blood is shunted to the body's core. This beneficial action comes with a significant negative consequence—increased cardiac irritability—which may lead to additional complications immediately following an otherwise successful resuscitation. Alternatives to this treatment include vasopressin, a powerful antidiuretic which also increases peripheral vascular resistance leading to blood shunting via vasoconstriction, but without the attendant increase to myocardial irritability.
- Because of its suppressive effect on the immune system, epinephrine is used to treat **anaphylaxis** and **sepsis**. Allergy patients undergoing immunotherapy may receive an epinephrine rinse before the allergen extract is administered, thus reducing the immune response to the administered allergen. It is also used as a bronchodilator for asthma if specific beta<sub>2</sub>-adrenergic receptor agonists are unavailable or ineffective. Adverse reactions to epinephrine include palpitations, tachycardia, anxiety, headache, tremor, hypertension, and acute **pulmonary edema**.

### **2.5.1-2. Noradrenalin Hormone:**

- **Norepinephrine** (INN) or **noradrenaline** (BAN) is a catecholamine and a phenethylamine with chemical formula C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub>. The natural stereoisomer is L-(–)-(R)-norepinephrine. It is released from the medulla of the adrenal glands as a hormone into the blood, but it is also a neurotransmitter in the central nervous system and sympathetic nervous system where it is released from noradrenergic

neurons during synaptic transmission. As a **stress hormone**, it affects parts of the human brain where attention and responding actions are controlled. Along with epinephrine, norepinephrine underlies the **fight-or-flight response**, directly increasing heart rate, triggering the release of glucose from energy stores, and increasing skeletal muscle readiness.

- Norepinephrine is released when a host of physiological changes are activated by a stressful event. This is caused in part by activation of an area of the brain stem called the locus ceruleus. This nucleus is the origin of most norepinephrine pathways in the brain. Neurons that are activated by norepinephrine project bilaterally (send signals to both sides of the brain) from the locus ceruleus along distinct pathways to many locations, including the cerebral cortex, limbic system, and the spinal cord.
- At synapses, norepinephrine acts on both alpha and beta adrenoreceptors.
- Norepinephrine is synthesized by a series of enzymatic steps in the adrenal medulla from the amino acid tyrosine:
  - The first reaction is the oxidation into dihydroxyphenylalanine (L-DOPA).
  - This is followed by decarboxylation into the neurotransmitter dopamine.
  - Last is the final  $\beta$ -oxidation into norepinephrine by dopamine beta hydroxylase.

## **Functions and clinical uses**

### **A) Attention-deficit/hyperactivity disorder**

- Norepinephrine, along with dopamine, has come to be recognized as playing a large role in attention and focus. For people with ADD/ADHD, psychostimulant medications such as Ritalin/Concerta (methylphenidate), Dexedrine (dextroamphetamine), and Adderall (a mixture of dextroamphetamine and racemic amphetamine salts) are prescribed to help increase levels of norepinephrine and dopamine. Strattera (atomoxetine) is a selective norepinephrine reuptake inhibitor, and is a unique ADD/ADHD medication, as it affects only norepinephrine, rather than dopamine. As a result, Strattera has a lower abuse potential. However, it may not be as effective as the psychostimulants are with many people who have ADD/ADHD.

### **B) Depression**

- Differences in the norepinephrine system are implicated in depression. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are antidepressants that treat depression by increasing the amount of serotonin and norepinephrine available to postsynaptic cells in the brain. There is some recent evidence showing that the norepinephrine transporter also transports some dopamine as well, implying that SNRIs may also increase dopamine transmission. This is because SNRIs work by inhibiting reuptake, i.e. preventing the serotonin and norepinephrine transporters from taking their respective neurotransmitters back to their storage vesicles for later use. If the norepinephrine transporter normally recycles some dopamine too, then SNRIs will also enhance dopaminergic transmission. Therefore, the

antidepressant effects associated with increasing norepinephrine levels may also be partly or largely due to the concurrent increase in **dopamine** (particularly in the prefrontal cortex).

- Tricyclic antidepressants (TCAs) increase **norepinephrine** as well. Most of them also increase serotonin, but tend to have a lot of side effects due to actions on receptors for histamine and acetylcholine. These include tiredness, increased hunger, dry mouth, and blurred vision. For this reason, they have largely been replaced by newer selective reuptake drugs.

### C) Vasopression

- Norepinephrine is also used as a vasopressor medication (for example, brand name Levophed) for patients with critical hypotension. It is given intravenously and acts on both alpha-1 and alpha-2 adrenergic receptors to cause vasoconstriction. Its effect in-vitro is often limited to the increasing of blood pressure through antagonising alpha-1 and alpha-2 receptors and causing a resultant increase in systemic vascular resistance. In high dose and especially when it is combined with other vasopressors, it can lead to limb ischemia and limb death.
- Norepinephrine is mainly used to treat patients in vasodilatory shock states such as Septic Shock and Neurogenic shock and has shown a survival benefit over dopamine.

### 2.5.1 Adrenal Cortex Hormones

- Situated along the perimeter of the adrenal gland, the **adrenal cortex** mediates the stress response through the production of mineralocorticoids and glucocorticoids, including aldosterone and cortisol respectively. It is also a secondary site of androgen synthesis
- The cortex can be divided into three distinct layers of tissue based on their organization.
- The most superficial cortical layer is the :

Layer	Name	Primary product
Most superficial cortical layer	zona glomerulosa	mineralocorticoids (eg, aldosterone)
Middle cortical layer	zona fasciculata	glucocorticoids (eg, cortisol)
Deepest cortical layer	zona reticularis	weak androgens (eg, dehydroepiandrosterone)

#### 2.5.1-1. Mineralocorticoids

- **Mineralocorticoids** is a class of *steroid hormones* characterised by their similarity to aldosterone and their influence on *salt and water balance*.

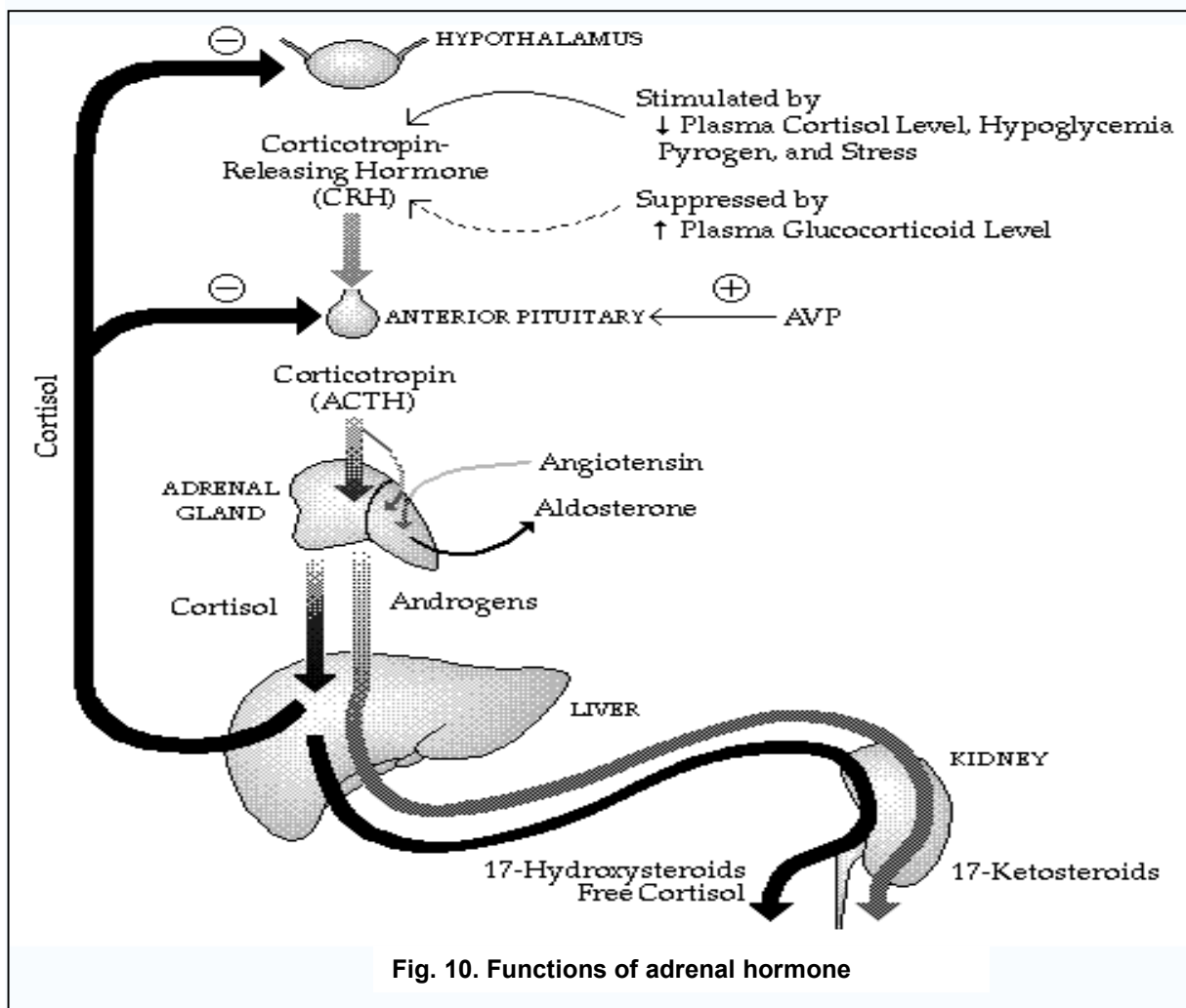
- The primary endogenous mineralocorticoid is **aldosterone**, although a number of other endogenous hormones (including progesterone and deoxycorticosterone) have mineralocorticoid function.
- Aldosterone acts on the kidneys to provide active **reabsorption of sodium** and an associated passive **reabsorption of water**, as well as, the active secretion of potassium in the principle cells of the cortical collecting tubule and active secretion of protons via proton ATPases in the luminal membrane of the intercalated cells of the collecting tubule. This in turn results in an increase of blood pressure and blood volume.
- Aldosterone is produced in the cortex of the adrenal gland and its secretion is mediated principally by **angiotensin II**, but also by adrenocorticotrophic hormone (ACTH) and local potassium levels.

### **Functions of Mineralocorticoids**

- Mineralocorticoids bind to the cytosolic mineralocorticoid receptor. This type of receptor gets activated upon ligand binding. After a hormone binds to the corresponding receptor, the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many hormone response elements (HRE) in the promoter region of the target genes in the DNA.
- The opposite mechanism is called **transrepression**. The hormone receptor without ligand binding interacts with heat shock proteins and prevents the transcription of targeted genes.
- Aldosterone and cortisol have similar affinity for the mineralocorticoid receptor however, glucocorticoids circulate at roughly 100 times the level of mineralocorticoids. An enzyme exists in mineralocorticoid target tissues to prevent overstimulation by glucocorticoids. This enzyme, 11-beta hydroxysteroid dehydrogenase type II (Protein:HSD11B2), catalyzes the deactivation of glucocorticoids to 11-dehydro metabolites. Licorice is known to be an inhibitor of this enzyme and chronic consumption can result in a condition known as pseudohyperaldosteronism

### **Clinical problems**

- **Hyperaldosteronism** (the syndrome caused by elevated aldosterone) generally results from adrenal neoplasms. The two main resulting problems:
  - 1) **Hypertension** and **edema** due to excessive Na<sup>+</sup> and water retention.
  - 2) Accelerated excretion of potassium ions. With extreme K<sup>+</sup> loss there is muscle weakness and eventually paralysis.
- **Underproduction**, or hypoaldosteronism, leads to the salt-wasting state associated with Addison's disease, although classical congenital adrenal hyperplasia and other disease states may also cause this situation.



### 2.5.1-2. Glucocorticoids

- **Glucocorticoids** are a class of steroid hormones characterised by an ability to bind with the cortisol receptor and trigger similar effects. Glucocorticoids are distinguished from mineralocorticoids and sex steroids by the specific receptors, target cells, and effects. Technically, the term *corticosteroid* refers to both glucocorticoids and mineralocorticoids, but is often used as a synonym for *glucocorticoid*.
- **Cortisol** (or hydrocortisone) is the most important human glucocorticoid. It is essential for life and regulates or supports a variety of important cardiovascular, metabolic, immunologic, and homeostatic functions. Glucocorticoid receptors are found in the cells of almost all vertebrate tissues.

#### **Functions of glucocorticoids**

- The name **glucocorticoid** derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, cortisol stimulates

several processes that collectively serve to increase and maintain normal concentrations of glucose in blood. These effects include:

- Stimulation of **gluconeogenesis**, particularly in the liver: This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.
- Mobilization of amino acids from extrahepatic tissues. These serve as substrates for gluconeogenesis.
- Inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose.
- Stimulation of **fat breakdown** in adipose tissue: The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.
- Glucocorticoids have potent **anti-inflammatory** and **immunosuppressive** properties. This is particularly evident when they are administered at pharmacological doses, but also is important in normal immune responses. As a consequence, glucocorticoids are widely used as drugs to treat inflammatory conditions such as arthritis or dermatitis, and as adjuvant therapy for conditions such as **autoimmune diseases**.
- Glucocorticoids have multiple effects on fetal development. An important example is their role in promoting maturation of the lung and production of the surfactant necessary for extrauterine lung function. Mice with homozygous disruptions in the corticotropin-releasing hormone gene die at birth due to pulmonary immaturity.
- Excessive glucocorticoid levels resulting from administration as a drug or **hyperadrenocorticism** have effects on many systems. Some examples include inhibition of bone formation, suppression of calcium absorption (both of which can lead to osteoporosis), delayed wound healing, muscle weakness and increased risk of infection. These observations suggest a multitude of less dramatic physiologic roles for glucocorticoids.

## ***Clinical problems***

### ***A) Medical uses and effects of high dose glucocorticoids***

- In much higher doses (termed *pharmacologic doses*), glucocorticoids are used to suppress various allergic, inflammatory, and autoimmune disorders. They are also administered as posttransplant immunosuppressants to prevent the acute transplant rejection and the graft-versus-host disease. Nevertheless, they do not prevent an infection and also inhibit later reparative processes.
- Some drugs used are cortisol (hydrocortisone), prednisone and dexamethasone.

**B) Immunosuppressive mechanism**

- Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8 and IFN- $\gamma$ , the most important of which is the IL-2. Smaller cytokine production reduces the T cell proliferation.
- Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B cell clone expansion and antibody synthesis. The diminished amounts of IL-2 also causes less T lymphocyte cells to be activated.
- Since glucocorticoid is a steroid, it regulates transcription factors; another factor it down regulates is the expression of Fc receptors on macrophages, so there is a decreased phagocytosis of opsonised cells.

**C) Antiinflammatory effects**

- Glucocorticoids influence all types of inflammatory events, no matter what their cause. They induce the lipocortin-1 (annexin-1) synthesis, which then binds to cell membranes preventing the phospholipase A2 from coming into contact with its substrate arachidonic acid. This leads to diminished eicosanoid production. The cyclooxygenase (both COX-1 and COX-2) expression is also suppressed, potentiating the effect. In other words, the two main products in inflammation Prostaglandins and Leukotrienes are inhibited by the action of Glucocorticoids.
- Glucocorticoids also stimulate the lipocortin-1 escaping to the extracellular space, where it binds to the leukocyte membrane receptors and inhibits various inflammatory events: epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators (lysosomal enzymes, cytokines, tissue plasminogen activator, chemokines etc.) from neutrophils, macrophages and mastocytes.

**D) Side effects**

- Glucocorticoid drugs currently being used act nonselectively, so in the long run they may impair many healthy anabolic processes. To prevent this, much research has been focused recently on the elaboration of selectively acting glucocorticoid drugs. These are the side effects that could be prevented:
  - immunosuppression
  - hyperglycemia due to increased gluconeogenesis, insulin resistance and impaired glucose tolerance ("steroid diabetes"); caution in those with diabetes mellitus
  - increased skin fragility, easy bruising
  - reduced bone density (osteoporosis, higher fracture risk, slower fracture repair)

- weight gain due to increased visceral and truncal fat deposition (central obesity) and appetite stimulation.
- adrenal insufficiency (if used for long time and stopped suddenly without a taper)
- muscle breakdown (proteolysis), weakness; reduced muscle mass and repair
- expansion of malar fat pads and dilation of small blood vessels in skin
- anovulation, irregularity of menstrual periods
- growth failure, pubertal delay
- increased plasma amino acids, increased urea formation; negative nitrogen balance
- excitatory effect on central nervous system

### 2.5.1-3. Androgens

- **Androgen** is the generic term for any natural or synthetic compound, usually a steroid hormone, that stimulates or controls the development and maintenance of masculine characteristics in vertebrates by binding to androgen receptors. This includes the activity of the accessory male sex organs and development of male secondary sex characteristics. Androgens, which were first discovered in 1936, are also called **androgenic hormones** or **testoids**. Androgens are also the original anabolic steroids. They are also the precursor of all estrogens, the female sex hormones. The primary and most well-known androgen is **testosterone**.
- A subset of androgens, **adrenal androgens**, includes any of the 19-carbon steroids synthesized by the adrenal cortex, the outer portion of the adrenal gland (zonula reticularis), that function as weak steroids or steroid precursors, including dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstenedione.
- Besides testosterone, other androgens include:
  - **Dehydroepiandrosterone** (DHEA): a steroid hormone produced from cholesterol in the adrenal cortex, which is the primary precursor of natural estrogens. DHEA is also called dehydroisoandrosterone or dehydroandrosterone.
  - **Androstenedione** (Andro): an androgenic steroid, which is produced by the testes, adrenal cortex, and ovaries. While androstenediones are converted metabolically to testosterone and other androgens, they are also the parent structure of estrone. Use of androstenedione as an athletic or body building supplement has been banned by the International Olympic Committee as well as other sporting organizations.
  - **Androstenediol**: the steroid metabolite that is thought to act as the main regulator of gonadotropin secretion.
  - **Androsterone**: a chemical by-product created during the breakdown of androgens, or derived from progesterone, that also exerts minor masculinising effects, but with one-seventh the intensity of testosterone. It is found in

approximately equal amounts in the plasma and urine of both males and females.

- **Dihydrotestosterone (DHT):** a metabolite of testosterone that is actually a more potent androgen in that it binds more strongly to androgen receptors.

### **Functions of Androgens:**

#### **A) Development of the male**

- During mammalian development, the gonads are at first capable of becoming either ovaries or testes<sup>[1]</sup>. In humans, starting at about week 4 the gonadal rudiments are present within intermediate mesoderm adjacent to the developing kidneys. At about week 6, epithelial sex cords develop within the forming testes and incorporate the germ cells as they migrate into the gonads. In males, certain Y chromosome genes, particularly SRY, control development of the male phenotype, including conversion of the early bipotential gonad into testes. In males, the sex cords fully invade the developing gonads.
- By week 8 of human fetal development, Leydig cells appear in the differentiating gonads of males. The mesoderm-derived epithelial cells of the sex cords in developing testes become the Sertoli cells which will function to support sperm cell formation. A minor population of non-epithelial cells exists between the tubules, these are the androgen-producing Leydig cells.
- The Leydig cells can be viewed as producers of androgens that function as paracrine hormones required by the Sertoli cells in order to support sperm production. Soon after they differentiate, Leydig cells begin to produce androgens which are required for masculinization of the developing male fetus (including penis and scrotum formation). Under the influence of androgens, remnants of the mesonephron, the Wolffian ducts, develop into the epididymis, vas deferens and seminal vesicles. This action of androgens is supported by a hormone from Sertoli cells, AMH, which prevents the embryonic Müllerian ducts from developing into fallopian tubes and other female reproductive tract tissues in male embryos. AMH and androgens cooperate to allow for the normal movement of testes into the scrotum.
- Before the production of the pituitary hormone LH by the embryo starting at about weeks 11-12, human chorionic gonadotrophin (hCG) promotes the differentiation of Leydig cells and their production of androgens. Androgen action in target tissues often involves conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT).

#### **B) Spermatogenesis**

- During puberty, androgen, LH and FSH production increase and the sex cords hollow out, forming the seminiferous tubules, and the germ cells start to differentiate into sperm. Throughout adulthood, androgens and FSH cooperatively act on Sertoli cells in the testes to support sperm production.

- Exogenous androgen supplements can be used as a male contraceptive. Elevated androgen levels caused by use of androgen supplements can inhibit production of LH and block production of endogenous androgens by Leideg cells. Without the locally high levels of androgens in testes due to androgen production by Leideg cells, the seminiferous tubules can degenerate resulting in infertility.

### C) Inhibition of fat deposition

- Males typically have less adipose tissue than females. Recent results indicate that androgens inhibit the ability of some fat cells to store lipids by blocking a signal transduction pathway that normally supports adipocyte function.

### D) Muscle mass

- Males typically have more skeletal muscle mass than females. Androgens promote the enlargement of skeletal muscle cells and probably act in a coordinated manner to enhance muscle function by acting on several cell types in skeletal muscle tissue.

### E) Brain

- Circulating levels of androgens can influence human behavior because some neurons are sensitive to steroid hormones. Androgen levels have been implicated in the regulation of human aggression and libido.

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## 2.6 PANCREATIC HORMONES

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- The **pancreas** is an organ in the digestive and endocrine system (of vertebrates). It is both exocrine (secreting pancreatic juice containing digestive enzymes) and endocrine (producing several important hormones, including **insulin**, **glucagon**, and **somatostatin**).
- In humans, the pancreas is a 15-25 cm (6-10 inch) elongated organ in the abdomen. One of the retroperitoneal organs, it is located posterior to the stomach and in close association with the duodenum.
- It is often described as having three regions: a head, body and tail.
  - The pancreatic head abuts the second part of the duodenum.
  - The body of the pancreas lies at the level of L2 on the spine.
  - The tail of the pancreas extends towards the spleen.
- The pancreatic duct (also called the duct of Wirsung<sup>[3]</sup>) runs the length of the pancreas and empties into the second part of the duodenum at the ampulla of Vater. The common bile duct usually joins the pancreatic duct at or near this point. Many people also have a small accessory duct, the duct of Santorini, which extends from the main duct more upstream (towards the tail) to the duodenum, joining it more proximal than the ampulla of Vater

- Under a microscope, when properly stained, it is easy to distinguish two different tissue types in the pancreas. These regions correspond to the main pancreatic functions:

Appearance	Region	Function
light staining circles (islets of Langerhans)	endocrine pancreas	secretes hormones that regulate blood glucose levels
darker surrounding tissue	exocrine pancreas	produces enzymes that break down digestible foods

### **Endocrine Function of Pancreas**

- There are four main types of cells in the islets of Langerhans. They are relatively difficult to distinguish using standard staining techniques, but they can be classified by their secretion:

Name of cells	Product	% of islet cells	Function
beta cells	Insulin and Amylin	50-80%	lower blood sugar
alpha cells	Glucagon	15-20%	raise blood sugar
delta cells	Somatostatin	3-10%	inhibit endocrine pancreas
PP cells	Pancreatic polypeptide	1%	inhibit exocrine pancreas

- The islets are a compact collection of endocrine cells arranged in clusters and cords and are crisscrossed by a dense network of capillaries.
- The capillaries of the islets are lined by layers of endocrine cells in direct contact with vessels, and most endocrine cells are in direct contact with blood vessels, by either cytoplasmic processes or by direct apposition.

### **Exocrine Function of Pancreas**

There are two main classes of exocrine pancreatic secretions:

Secretion	Cell producing it	Primary signal
bicarbonate ions	Centroacinar cells	Secretin
digestive enzymes (pancreatic amylase, trypsin, chymotrypsin, etc.)	Basophilic cells	CCK

### 2.6.1 Insulin Hormone

- **Insulin** (from Latin *insula*, "island", as it is produced in the Islets of Langerhans in the pancreas) is a polypeptide hormone that regulates carbohydrate metabolism. Apart from being the primary agent in carbohydrate homeostasis, it has effects on fat metabolism and it changes the liver's activity in storing or releasing glucose and in processing blood lipids, and in other tissues such as fat and muscle. The amount of insulin in circulation has extremely widespread effects throughout the body.
- In mammals, insulin is synthesized in the pancreas within the beta cells ( $\beta$ -cells) of the islets of Langerhans. One to three million islets of Langerhans (pancreatic islets) form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine portion only accounts for 2% of the total mass of the pancreas. Within the islets of Langerhans, beta cells constitute 60–80% of all the cells.
- Insulin is used medically to treat some forms of diabetes mellitus. Patients with type 1 diabetes mellitus depend on external insulin (most commonly injected subcutaneously) for their survival because of an absolute deficiency of the hormone. Patients with type 2 diabetes mellitus have insulin resistance, relatively low insulin production, or both; some type 2 diabetics eventually require insulin when other medications become insufficient in controlling blood glucose levels.
- Insulin is composed of 51 amino acid residues and has a molecular weight of 5808 Da.
- Insulin's structure varies slightly between species of animal. Insulin from animal sources differs somewhat in regulatory function strength (ie, in carbohydrate metabolism) in humans because of those variations. Porcine (pig) insulin is especially close to the human version.

### Functions of Insulin

#### A) Actions on cellular and metabolic level

- The actions of insulin on the global human metabolism level include:
  - Control of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about  $\frac{2}{3}$  of body cells).
  - Increase of DNA replication and protein synthesis via control of amino acid uptake.
  - Modification of the activity of numerous enzymes (allosteric effect).
- The actions of insulin on cells include:
  - Increased glycogen synthesis – insulin forces storage of glucose in liver (and muscle) cells in the form of glycogen; lowered levels of insulin cause liver cells to convert glycogen to glucose and excrete it into the blood. This is the clinical action of insulin which is directly useful in reducing high blood glucose levels as in diabetes.
  - Increased fatty acid synthesis – insulin forces fat cells to take in blood lipids which are converted to triglycerides; lack of insulin causes the reverse.

- Increased esterification of fatty acids – forces adipose tissue to make fats (ie, triglycerides) from fatty acid esters; lack of insulin causes the reverse.
- Decreased proteinolysis – forces reduction of protein degradation; lack of insulin increases protein degradation.
- Decreased lipolysis – forces reduction in conversion of fat cell lipid stores into blood fatty acids; lack of insulin causes the reverse.
- Decreased gluconeogenesis – decreases production of glucose from various substrates in liver; lack of insulin causes glucose production from assorted substrates in the liver and elsewhere.
- Increased amino acid uptake – forces cells to absorb circulating amino acids; lack of insulin inhibits absorption.
- Increased potassium uptake – forces cells to absorb serum potassium; lack of insulin inhibits absorption.
- Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in micro arteries; lack of insulin reduces flow by allowing these muscles to contract.

### **B) Regulatory action on blood glucose**

- Despite long intervals between meals or the occasional consumption of meals with a substantial carbohydrate load (e.g., half a birthday cake or a bag of potato chips), human blood glucose levels normally remain within a narrow range. In most humans this varies from about 70 mg/dl to perhaps **110 mg/dl** (3.9 to 6.1 mmol/litre) except shortly after eating when the blood glucose level rises temporarily. This homeostatic effect is the result of many factors, of which hormone regulation is the most important.
- It is usually a surprise to realize how little glucose is actually maintained in the blood, and body fluids. The control mechanism works on very small quantities. In a healthy adult male of 75 kg with a blood volume of 5 litres, a blood glucose level of 100 mg/dl or 5.5 mmol/l corresponds to about 5 g (1/5 ounce) of glucose in the blood and approximately 45 g (1½ ounces) in the total body water (which obviously includes more than merely blood and will be usually about 60% of the total body weight in men). A more familiar comparison may help -- 5 grams of glucose is about equivalent to a commercial sugar packet (as provided in many restaurants with coffee or tea).
- There are two types of mutually antagonistic metabolic hormones affecting blood glucose levels:
  - Catabolic hormones (such as glucagon, growth hormone, and catecholamines), which increase blood glucose
  - and one anabolic hormone (insulin), which decreases blood glucose
- Mechanisms which restore satisfactory blood glucose levels after hypoglycemia must be quick, and effective, because of the immediate serious consequences of insufficient glucose (in the extreme, coma, less immediately dangerously, confusion or unsteadiness, amongst many other effects). This is because, at least in the short term, it is far more dangerous to have too little glucose in the blood than too much. In healthy individuals these mechanisms are indeed generally efficient, and symptomatic hypoglycemia is generally only found in diabetics using insulin or other

pharmacologic treatment. Such hypoglycemic episodes vary greatly between persons and from time to time, both in severity and swiftness of onset. In severe cases prompt medical assistance is essential, as damage (to brain and other tissues) and even death will result from sufficiently low blood glucose levels.

### **Clinical problems**

- There are several conditions in which insulin disturbance is pathologic:
  - **Diabetes mellitus** – general term referring to all states characterized by hyperglycemia.
    - Type 1 – autoimmune-mediated destruction of insulin producing beta cells in the pancreas resulting in absolute insulin deficiency.
    - Type 2 – multifactorial syndrome with combined influence of genetic susceptibility and influence of environmental factors, the best known being obesity, age, and physical inactivity, resulting in insulin resistance in cells requiring insulin for glucose absorption. This form of diabetes is strongly inherited.
    - Other types of impaired glucose tolerance (see the diabetes article).
  - **Insulinoma** or reactive hypoglycemia.
  - **Metabolic syndrome** – a poorly understood condition first called Syndrome X by Gerald Reaven, Reaven's Syndrome after Reaven, CHAOS in Australia (from the signs which seem to travel together), and sometimes prediabetes. It is currently not clear whether these signs have a single, treatable cause, or are the result of body changes leading to type 2 diabetes. It is characterized by elevated blood pressure, dyslipidemia (disturbances in blood cholesterol forms and other blood lipids), and increased waist circumference (at least in populations in much of the developed world). The basic underlying cause may be the insulin resistance of type 2 diabetes which is a diminished capacity for insulin response in some tissues (eg, muscle, fat) to respond to insulin. Commonly, morbidities such as essential hypertension, obesity, Type 2 diabetes, and cardiovascular disease (CVD) develop.
  - **Polycystic ovary syndrome** – a complex syndrome in women in the reproductive years where there is anovulation and androgen excess commonly displayed as hirsutism. In many cases of PCOS insulin resistance is present

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### **2.6.2. Glucagon Hormone**

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- **Glucagon** is a 29-amino acid polypeptide acting as an important hormone in carbohydrate metabolism. The polypeptide has a molecular weight of 3485 daltons and was discovered in 1923 by Kimball and Murlin.
- Its primary structure in humans is: NH<sub>2</sub>-His-Ser-Gln-Gly-Thr-Phe- Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser- Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu- Met-Asn-Thr-COOH

- The hormone is synthesized and secreted from alpha cells ( $\alpha$ -cells) of the islets of Langerhans, which are located in the endocrine portion of the pancreas. The alpha cells are located in the outer rim of the islet.

### **Functions of Glucagon:**

- Glucagon helps maintain the level of glucose in the blood by binding to glucagon receptors on hepatocytes, causing the liver to release glucose - stored in the form of glycogen - through a process known as glycogenolysis. As these stores become depleted, glucagon then encourages the liver to synthesize additional glucose by gluconeogenesis. This glucose is released into the bloodstream. Both of these mechanisms lead to glucose release by the liver, preventing the development of hypoglycemia.
  - Increased free fatty acids and ketoacids into the blood
  - Increased urea production
- An injectable form of glucagon is essential first aid in cases of severe hypoglycemia, usually in a dose of 1 milligram. The glucagon is given by intramuscular injection, and quickly raises blood glucose levels. Glucagon can be administered IV at 0.25 - 0.5 unit.
- Anecdotal evidence suggests a benefit of higher doses of glucagon in the treatment of overdose with beta blockers; the likely mechanism of action is the increase of cAMP in the myocardium, effectively bypassing the inhibitory action of the  $\beta$ -adrenergic second messenger system

### **Clinical problems**

- Abnormally-elevated levels of glucagon may be caused by pancreatic tumors such as **glucagonoma**, symptoms of which include necrolytic migratory erythema (NME), elevated amino acids and hyperglycemia. It may occur alone or in the context of multiple endocrine **neoplasia** type 1.

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### **2.6.3. Somatostatin Hormone**

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- **Somatostatin** (also known as **Growth Hormone Inhibiting Hormone**) is a peptide hormone that regulates the endocrine system and affects neurotransmission and cell proliferation via interaction with G-protein-coupled somatostatin receptors and inhibition of the release of numerous secondary hormones.
- Somatostatin has two active forms produced by alternative cleavage of a single preproprotein: one of 14 amino acids, the other of 28 amino acids.

### **Functions of somatostatin**

- Somatostatin is classified as an inhibitory hormone,<sup>[1]</sup> whose main actions are to:

- Inhibit the release of growth hormone (GH)<sup>[2]</sup> (thus opposing the effects of Growth Hormone-Releasing Hormone (GHRH))
- Inhibit the release of thyroid-stimulating hormone (TSH)
- Suppress the release of gastrointestinal hormones
  - Gastrin
  - Cholecystokinin (CCK)
  - Secretin
  - Motilin
  - Vasoactive intestinal peptide (VIP)
  - Gastric inhibitory polypeptide (GIP)
  - Enteroglucagon (GIP)
- Lowers the rate of gastric emptying, and reduces smooth muscle contractions and blood flow within the intestine
- Suppress the release of pancreatic hormones
  - Inhibit the release of insulin
  - Inhibit the release of glucagon
- Suppress the exocrine secretory action of pancreas.

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## 1.6 GONADAL HORMONES

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- The male and female **gonads** produce steroid sex hormones, identical to those produced by adrenal cortical cells. The major distinction is the source and relative amounts produced
- Gonads start developing as a common anlage, and only later are differentiated to male or female sex organs: male gonads (testicles) or female gonads (ovaries).
- In males, the male gonads, known as the testes or testicles, secrete the class of hormones called androgens, and produce spermatazoa. The predominant androgen in males is testosterone. In females, the female gonads, known as the ovaries, secrete the hormones estrogen and progesterone, as well as ova. The dominant estrogen is known as estradiol, which is derived from testosterone

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### 1.6.1 Male Gonadal Hormone: Testosterone:

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- **Testosterone** is a steroid hormone from the androgen group. Testosterone is primarily secreted in the testes of males and the ovaries of females although small amounts are secreted by the adrenal glands. It is the principal male sex hormone and an anabolic steroid. In both males and females, it plays key roles in health and well-being. Examples include enhanced libido, energy, immune function, and protection against **osteoporosis**. On average, the adult male body produces about twenty to thirty times the amount of testosterone that an adult female's body does

#### ***Functions of Testosterone:***

### A) Anabolic effects on humans

- In general, androgens promote protein synthesis and growth of those tissues with androgen receptors. Testosterone effects can be classified as *virilizing* and *anabolic effects*, although the distinction is somewhat artificial, as many of the effects can be considered both.
- *Anabolic effects* include growth of muscle mass and strength, increased bone density and strength, and stimulation of linear growth and bone maturation.
- *Virilizing effects* include maturation of the sex organs, particularly the penis and the formation of the scrotum in fetuses, and after birth (usually at puberty) a deepening of the voice, growth of the beard and axillary hair. Many of these fall into the category of male secondary sex characteristics.
- Testosterone effects can also be classified by the age of usual occurrence. For postnatal effects in both males and females, these are mostly dependent on the levels and duration of circulating free testosterone.

### B) Prenatal androgen effects

- Most of the *prenatal androgen effects* occur between 7 and 12 weeks of gestation.
  - Genital virilization (midline fusion, phallic urethra, scrotal thinning and rugation, phallic enlargement)
  - Development of prostate and seminal vesicles

### C) Early infancy androgen effects

- *Early infancy androgen effects* are the least understood. In the first weeks of life for male infants, testosterone levels rise. The levels remain in a pubertal range for a few months, but usually reach the barely detectable levels of childhood by 4-6 months of age. The function of this rise in humans is unknown. It has been speculated that "brain masculinization" is occurring since no significant changes have been identified in other parts of the body.

### D) Early postnatal effects

- *Early postnatal effects* are the first visible effects of rising androgen levels in childhood, and occur in both boys and girls in puberty.
  - Adult-type body odour
  - Increased oiliness of skin and hair, acne
  - Pubarche (appearance of pubic hair)
  - Axillary hair
  - Growth spurt, accelerated bone maturation
  - Fine upper lip and sideburn hair

### E) Advanced postnatal effects

- *Advanced postnatal effects* begin to occur when androgen has been higher than normal adult female levels for months or years. In males these are normal late pubertal effects, and only occur in women after prolonged periods of excessive levels of free testosterone in the blood.
  - Phallic enlargement (including clitoromegaly)
  - Increased libido and erection frequency
  - Pubic hair extends to thighs and up toward umbilicus
  - Facial hair (sideburns, beard, moustache)
  - Chest hair, periareolar hair, perianal hair
  - Subcutaneous fat in face decreases
  - Increased muscle strength and mass
  - Deepening of voice
  - Growth of the adam's apple
  - Growth of spermatogenic tissue in testes, male fertility
  - Growth of jaw, brow, chin, nose, and remodeling of facial bone contours
  - Shoulders widen and rib cage expands
  - Completion of bone maturation and termination of growth. This occurs indirectly via estradiol metabolites and hence more gradually in men than women.

#### **F) Adult testosterone effects**

- *Adult testosterone effects* are more clearly demonstrable in males than in females, but are likely important to both sexes. Some of these effects may decline as testosterone levels decline in the later decades of adult life.
  - Maintenance of muscle mass and strength
  - Maintenance of bone density and strength
  - Libido and erection frequency.
  - Mental and physical energy

#### **G) Effect on Brain**

- As testosterone affects the entire body (often by enlarging; men have bigger hearts, lungs, liver, etc.) the brain is also affected by this "sexual" advancement; the enzyme aromatase converts testosterone into estrogen that is responsible for masculinization of the brain in a male fetus. Factors that in any way reduce aromatase can result in an individual with male gender, male body but with a "female" brain.
- There are some differences in a male and female brain (the result of testosterone); a clear difference is the size, the male human brain is on average larger, however in females (that do not use testosterone as much) the corpus callosum is proportionally larger. This means that the effect of testosterone is a greater overall brain volume, but a decreased connection between the hemispheres. It has suggested that alcohol consumption in women can temporarily raise testosterone levels. A 2006 BBC article states: "According to medical research, testosterone - the hormone connected to male

characteristics such as aggression and sex drive - rises in women by up to 50% when they get drunk. In men, it falls.

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### 1.6.2. Female Gonadal (Ovarian) Hormones:

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- In females, the female gonads, known as the ovaries, secrete the hormones estrogen and progesterone,

#### 1.6.2-1. Estrogen Hormone

- **Estrogens** (alternate spellings: **oestrogens** or **œstrogens**) are a group of steroid compounds, named for their importance in the **estrous cycle**, and functioning as the primary female sex hormone.
- Estrogens are used as part of some oral contraceptives and also in estrogen replacement therapy of postmenopausal women.
- Like all steroid hormones, estrogens readily diffuse across the cell membrane; inside the cell, they interact with estrogen receptors
- The three major naturally occurring estrogens in women are **estradiol**, **estriol**, and **estrone**. In the body these are all produced from androgens through actions of enzymes.
- From menarche to menopause the primary estrogen is 17 $\beta$ -estradiol. In postmenopausal women more estrone is present than estradiol.
- Estradiol is produced from testosterone and estrone from androstenedione
- Estrone is weaker than estradiol.
- A range of synthetic and natural substances have been identified that also possess estrogenic activity. Synthetic substances of this kind are known as xenoestrogens, while natural plant products with estrogenic activity are called phytoestrogens.
- Estrogen is produced primarily by developing follicles in the ovaries, the corpus luteum, and the placenta. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) stimulate the production of estrogen in the ovaries. Some estrogens are also produced in smaller amounts by other tissues such as the liver, adrenal glands, and the breasts. These secondary sources of estrogen are especially important in postmenopausal women.
- Synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of moderate androgenic activity. This compound crosses the basal membrane into the surrounding granulosa cells, where it is converted to estrone or estradiol, either immediately or through testosterone. The conversion of testosterone to estradiol, and of androstenedione to estrone, is catalyzed by the enzyme aromatase.

#### **Functions of estrogen:**

- While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. They promote the development of female secondary sex characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. In males estrogen regulates certain functions of the reproductive system important to the maturation of sperm. and may be necessary for a healthy libido
- Estradiol levels vary through the menstrual cycle, with levels highest just before ovulation.
- Structural
  - promote formation of female secondary sex characteristics
  - stimulate endometrial growth
  - increase uterine growth
  - maintenance of vessel and skin
  - reduce bone resorption, increase bone formation
- protein synthesis
  - increase hepatic production of binding proteins
- coagulation
  - increase circulating level of factors 2,7,9,10, antithrombin III, plasminogen
  - increase platelet adhesiveness
- Lipid
  - increase HDL, triglyceride, fat deposition
  - decrease LDL
- Fluid balance
  - salt and water retention
- gastrointestinal tract
  - reduce bowel motility
  - increase cholesterol in bile
- Cancer
  - About 80% of breast cancers, once established, rely on supplies of the hormone estrogen to grow: they are known as hormone-sensitive or hormone-receptor-positive cancers.<sup>[6]</sup> Suppression of production in the body of estrogen is a treatment for these cancers.
- Studies have found better correlation between sexual desire and androgen levels than for estrogen levels.<sup>[7]</sup>
- In studies involving mice and rats, it was found that lung function may be improved by estrogen. In one study involving 16 animals, female mice that had their ovaries removed to deprive them of estrogen lost 45 percent of their working alveoli from their lungs. Upon receiving estrogen, the mice recovered full lung function
- Estrogen is also used in the therapy of vaginal atrophy, hypoestrogenism (as a result of hypogonadism, castration, or primary ovarian failure), amenorrhea,

dysmenorrhea, and oligomenorrhea. Estrogens can also be used to suppress lactation after child birth.

### 1.6.2-2. Progesterone Hormone:

- **Progesterone** is a C-21 steroid hormone involved in the female menstrual cycle, pregnancy (supports *gestation*) and embryogenesis of humans and other species. Progesterone belongs to a class of hormones called progestogens, and is the major naturally occurring human progestogen.
- Progesterone should not be confused with progestins, which are synthetically produced progestogens.
- Progesterone is produced in the adrenal glands, the gonads (specifically after ovulation in the corpus luteum), the brain, and, during pregnancy, in the placenta.
- In humans, increasing amounts of progesterone are produced during pregnancy:
  - Initially, the source is the corpus luteum that has been "rescued" by the presence of human chorionic gonadotropins (hCG) from the conceptus.
  - However, after the 8th week production of progesterone shifts over to the placenta. The placenta utilizes maternal cholesterol as the initial substrate, and most of the produced progesterone enters the maternal circulation, but some is picked up by the fetal circulation and is used as substrate for fetal corticosteroids. At term the placenta produces about 250 mg progesterone per day
- In women, progesterone levels are relatively low during the preovulatory phase of the menstrual cycle, rise after ovulation, and are elevated during the luteal phase. In women progesterone levels tend to be < 2 ng/ml prior to ovulation, and > 5 ng/ml after ovulation. If pregnancy occurs, progesterone levels are maintained at luteal levels initially. With the onset of the luteal-placental shift in progesterone support of the pregnancy levels start to rise further and may reach 100-200 ng/ml at term. Whether a decrease in progesterone levels is critical for the initiation of labor has been argued and may be species-specific. After delivery of the placenta and during lactation, progesterone levels are very low.

### Functions of Progesterone:

- Progesterone exerts its action primarily through the intracellular progesterone receptor though a distinct, membrane bound progesterone receptor has recently been discovered. It has a number of physiological effects, often regulatory, not least of the effects of estrogen. Estrogen often induces a multiplication of progesterone receptors.

#### A) Reproductive system

- Progesterone is sometimes called the "hormone of pregnancy", and it has many roles relating to the development of the fetus:

- Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus. If pregnancy does not occur, progesterone levels will decrease, leading, in the human, to menstruation. Normal menstrual bleeding is progesterone withdrawal bleeding.
- During implantation and **gestation**, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy.
- Progesterone decreases contractility of the **uterine smooth muscle**.
- In addition progesterone inhibits **lactation** during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production.
- A drop in progesterone levels is possibly one step that facilitates the onset of labor.
- The fetus metabolizes placental progesterone in the production of adrenal mineralo- and glucosteroids.

### B) Nervous system

- Progesterone, like pregnenolone and dehydroepiandrosterone, belongs to the group of neurosteroids that are found in high concentrations in certain areas in the brain and are synthesized there.
- Neurosteroids affect synaptic functioning, are neuroprotective, and affect myelination. They are investigated for their potential to improve memory and cognitive ability.
- Progesterone as a neuroprotectant affects regulation of apoptotic genes.
- Its effect as a neurosteroid works predominantly through the GSK-3 beta pathway, as an inhibitor. (Other GSK-3 beta inhibitors include bipolar mood stabilizers, lithium and valproic acid.)

### C) Other systems

- It raises epidermal growth factor-1 levels, a factor often used to induce proliferation, and used to sustain cultures of stem cells.
- It reduces core temperature (thermogenic function).
- It reduces spasm and relaxes smooth muscle. Bronchi are widened and mucus regulated. (Progesterone receptors are widely present in submucosal tissue).
- It acts as an antiinflammatory agent and regulates the immune response.
- It reduces gall-bladder activity.
- It normalizes blood clotting and vascular tone, zinc and copper levels, cell oxygen levels, and use of fat stores for energy.

### 3. MECHANISM OF HORMONE ACTION

#### 3.1 INTRODCUTION

#### 3.2 HORMONE ACTION BY SECOND MESSENGER

#### 3.3 HORMONE ACTION BY ACTIVATION OF THE GENES

### 3.1 INTRODCUTION

- Although the physiological apparently secondary effects of most of the hormones have been rather completely known for a number of years, their primary biochemical mechanisms of actions at a cellular/molecular level are also known in much detail now.
- Many hormones serve as a inducers or repressors in the genetically controlled synthesis of certain key cellular enzymes.
- Although the exact site of action of any hormone is still not well understood, the following mechanisms of actions of a hormone have been proposed.

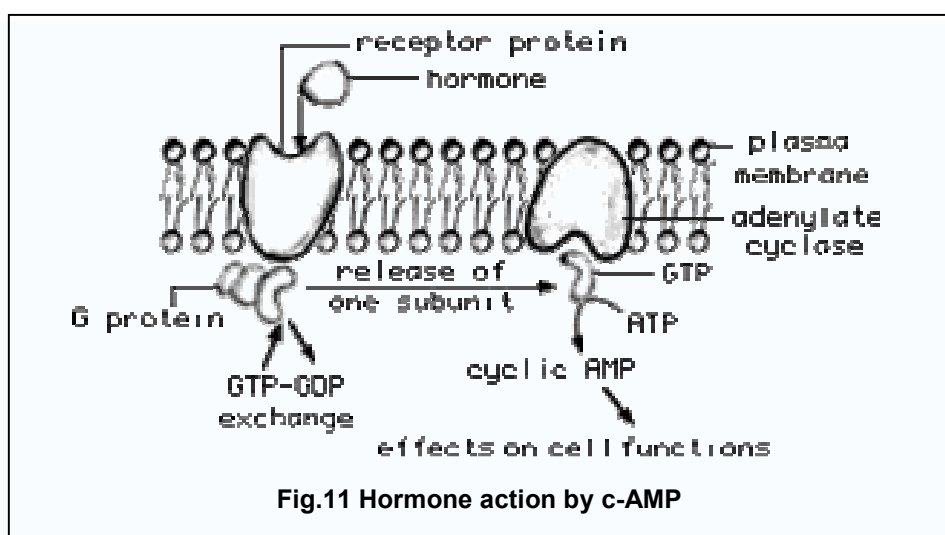
### 3.2. HORMONE ACTION BY THE SECOND MESSENGER

- Since proteins or peptide hormones cannot cross the cell membrane they must rely on activating their receptor on the target cell.
- Once hormone bound to the receptor, this will cause the production of a **second messenger**. Second messenger is a chemical that is either produced or released as the result of a hormone binding to the receptor on the cell membrane. It affects the activities of the **intracellular enzymes**. Due to the presence of second messengers, large intracellular changes are caused by small amounts of hormone.
- Cyclic AMP, Calcium, C-GMP, Calmuludin etc, are the examples of second messengers..
- Most of the protein and peptide hormones exert their effects on cells by first causing cyclic AMP to be formed in the cell. Once formed, the cyclic AMP initiates the desired activities inside the cell. Thus, cyclic AMP is said to be an **intracellular hormonal mediator**. It is also frequently called the '**second messenger**' for hormone mediation- the 'first messenger' being the original stimulating hormone.
- Mechanism of Hormone action by cyclic AMP second messenger has following steps:
  - Step-I: The first event in this mechanism of hormonal control is the action of the stimulating hormone on a specific receptor in the cell membrane. In fact, whether or not the hormone will affect a particular cell is determined by the presence or absence of this specific receptor for that hormone.
  - Step-II: Once the hormone binds with the receptor, an enzyme in the cell membrane called **adenyl cyclase** is activated.

Step-III: The adenyl cyclase then converts some of the **adenosine triphosphate** (ATP) inside the cell cytoplasm into cyclic AMP. The cyclic AMP persists in the cell for a few seconds to many minutes before it is reconverted into ATP. However, as long as the stimulating hormone remains active at the receptor, still more cyclic AMP will continue to be formed.

Step-IV: Once generated inside the cell, the cyclic AMP in turn performs any number

- Activating enzymes
  - Altering cell permeability
  - Altering the degree of smooth muscle contraction
  - Activating protein synthesis
  - Causing secretion by the cell
- The specific effect that occurs in each individual cell is determined by the characteristics of the cell. Thus, if the cell is a glandular cell, it will form its specific secretion; or if the cell is a smooth muscle cell, it will contract or relax depending upon whether the cyclic AMP is excitatory or inhibitory in that particular cell.
  - The cyclic AMP mechanism has been shown to act as an intracellular hormonal mediator system for at least some of the functions of each of the following hormones;
    - ACTH Hormone
    - TSH Hormone
    - Gonadotropic hormones, which stimulate the sex glands
    - Antidiuretic hormone
    - Parathyroid hormone, which controls extra cellular fluid calcium
    - Glucagons, which helps to control blood glucose concentration
    - Epinephrine, which controls contraction of many smooth muscles



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### 3.3. Hormone action by Activation of the genes:

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- A second important way in which hormones act is to activate one or more genes in the **nucleus**; these in turn cause synthesis of proteins in the target cells. This is the mechanism of hormonal control utilized by the steroid hormones secreted by the adrenal cortex, the ovaries, and the testicles.
- The general mechanism of steroid hormone function is the following steps:

Step-I: The hormone enters the cytoplasm of the cell where it combines with specific receptor protein.

Step-II: After several additional steps that occur in the cytoplasm and nucleus, one or more specific genes are activated in the nucleus.

Step-III: The genes cause the formation of specific messenger RNA molecules

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### 3.4 MEMBRANE RECEPTORS

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- Certain molecules cannot enter target cells through the membrane lipid bilayer. This is achieved by the specific receptor molecules present on the surface of the plasma membrane.
- Many hormones are specifically involved in the transport of a variety of substances across cell membrane.
- In general these hormones specifically bind to the receptors on cell membrane. They cause rapid secondary metabolic changes in the tissue but have little effect on metabolic activity of membrane-free preparations.
- Most protein hormones and catecholamine activate transport of membrane enzyme systems by direct binding to specific receptors on the membrane.

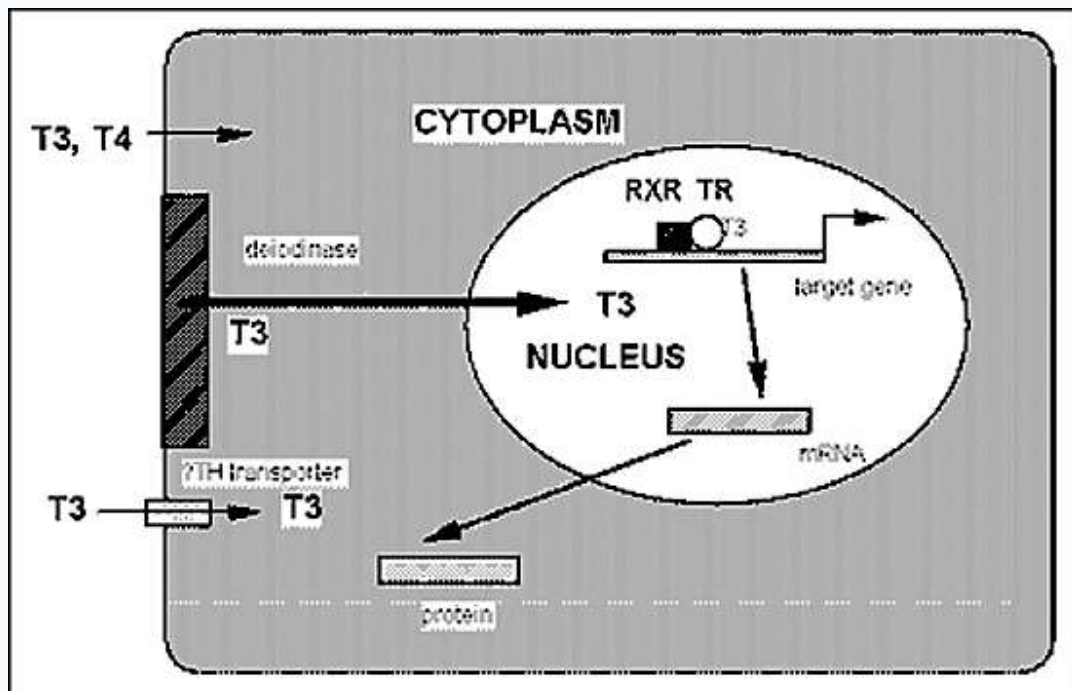
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### 3.5 ROLE OF CALCIUM IN HORMONE ACTION

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- The action of most protein hormones is inhibited in absence of calcium even though ability to increase or decrease cAMP is comparatively unimpaired. Thus calcium may be more terminal signal for hormones action than cAMP.
- It is suggested that ionized calcium of the cytosol is the important signal. The source of this calcium may be extracellular fluid or it may arise from mobilization of intracellular tissue bound calcium.
- The hormone receptor binding may directly inhibit the calcium-ATPase. It may
- The receptor hormone complex may produce IP<sub>3</sub> which in turn can increase cytosolic calcium concentration by enhancing the mobilization of calcium from mitochondrial and endoplasmic reticular pools.  
also directly open up voltage independent calcium channels in the membrane to increase the diffusion of calcium into the cell down its inward concentration

gradient resulting in increased cytosolic calcium concentration which then acts as a second messenger to affect cellular activities.



**Fig.12** Thyroid hormone action by gene level